

# YEAR REPORT 2009

DEPARTMENT OF ENDOCRINOLOGY

INTERNAL MEDICINE

University Medical Center Groningen



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## 1. Personnel

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

In this year report we will summarize our activities during the year 2009. After its success last years, this is the 4th year that our year report appears in English. Reasons for this are our increasing international contacts and collaborations.

In 2009 the following persons were members of our department:

Mrs. N. Alma - Bierma (Natasja)	secretary
Dr. A.P. van Beek (André)	internist-endocrinologist
Dr. G. van den Berg (Gerrit)	internist-endocrinologist
Mrs. B.T. de Boer (Berber)	diabetes nurse specialist
Mrs. E. van Driesum (Els)	diabetes nurse specialist
Dr. R.P.F. Dullaart (Robin)	internist-endocrinologist
Mrs. W. van El, MA (Winnie)	nurse practitioner
Mrs. M.A. Groeneveld (Mariska)	research assistant
Mrs. B.G. Haandrikman (Bettine)	medical analyst
Mrs. I. Hoekstra (Immie) until May	diabetes nurse specialist
Mrs. Dr. A.N.A. van der Horst - Schrivvers (Anouk)	internist-endocrinologist
Mrs. K.B.M. Janson (Carla)	diabetes nurse specialist
Mrs. A.B. Jongbloed (Alied)	diabetes nurse specialist
Dr. J.C. Keers (Joost), until October	psychologist
Dr. M.N. Kerstens (Michiel)	internist-endocrinologist
Mrs. dr. M.M. van der Klauw (Melanie)	internist-endocrinologist
Mrs. G. Kreugel, MSC (Gillian)	nursing consultant
Mrs. prof. dr. T.P. Links (Thera)	internist-endocrinologist
Mrs. dr. H. Lutgers (Helen)	internist-endocrinologist in training
Mrs. C. Neperus (Carolien) until May	secretary
Mrs. S.M. Pathuis (Susanne)	diabetes nurse specialist
Mrs. I.E. Pop (Inge)	physicians' assistant
Dr. W.J. Sluiter (Wim)	biochemist, statistician
Drs. F.A.J. Verburg (Erik Jan)	internist-endocrinologist
Mrs. R. Visser (Rosalie) until August	researcher
Prof. dr. B.H.R. Wolffenbuttel (Bruce)	internist-endocrinologist
Mrs. R. Zuur (Roelie) until February	diabetes nurse specialist

## **2. Developments in 2009**

In 2009 there were several developments within our department.

### **Staff members**

Dr. Thera Links has been appointed as professor of Endocrinology, in particular 'Familial Endocrine Tumoursyndromes'. This was effected in April 2009.

We welcomed Mrs. Els van Driesum, diabetes nurse specialist, who will be leading the educational activities of the diabetes nurses in the University Diabetes Center. Mrs. I. Hoekstra (Immie) and Mrs. R. Zuur (Roelie) left the department. Immie continued her work as diabetes nurse specialist in a large GP practice in the city of Groningen (Lewenborg), and Roelie started a new job as nurse at the First Aid department of the hospital of Delfzijl. Carolien Neperus, secretary, changed her field of work completely and joined the training to become a police officer. Joost Keers and Rosalie Visser left the department and continued their work as research staff members within the LifeLines Cohort Study and Biobank.

### **PhD thesis**

Members of the department were involved in several PhD theses, which were defended in 2009.

On February 11, Mr. Rindert de Vries defended his thesis titled "Lipid transfer proteins: consequences for cellular cholesterol efflux and cardiovascular risk in diabetes mellitus". Barely one month later, on March 4, Mrs. Adriëne Persoon defended her thesis entitled "New insights in the follow-up of differentiated thyroid carcinoma". She will start her training in Endocrinology in February 2010.



### **3. Health care / patient activities**

#### ***Clinic Ward E4***

The number of patients admitted to our ward E4 was 269, exactly the same as it was in 2008. Yet this number remains lower than in the years 2003-2005, probably related to the fact that we share the same beds with the Acute Care ward of the Department of Internal Medicine, and a strong demand for admissions for Internal Medicine reduces the possibilities for our department. The total number of beds for admission of patients with internal medicine disease is not sufficient, and especially during the fall and winter months many of our patients have to be admitted on other departments, like Neurology, Obstetrics and Surgery. With the introduction of new endoscopic techniques, most patients after pituitary surgery now remain 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..

Those 270 patients stayed in the ward for a total of 1550 days, implicating a stable average stay of 5.7 days. This short admission time is the result of efficient and careful planning of hospital discharge and outpatient follow-up. Nevertheless, a significant number of patients needed a hospital stay of more than 30 days. Mostly, these were patients with severe diabetic foot problems.

#### ***Outpatient clinic***

The number of outpatient clinic visit increased further in 2009. The number of patients seen for the first time has increased by over 10%. 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 are made in writing, and judged 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.

Also this year we are faced with a 4% 'no show' result. This means that on average in one of 25 appointments patients do not show up for their initial or follow-up visit, and this time lost puts other patients later in the waiting list. For this reason we have continued to make telephone calls to all patients who do not show up for their appointment, in order to reduce future 'no-shows'.

Table 1. Patient care activities of the department of Endocrinology

<b>Year</b>	<b>Clinic admissions</b>	<b>Outpatient clinic visits</b>	<b>First consultations outpatient-clinic</b>
2000	326	8796	494
2001	278	8198	512
2002	281	8360	570
2003	330	8815	642
2004	315	9720	761
2005	322	10148	705
2006	283	9631	812
2007	260	9761	958
2008	270	10421	973
2009	269	11070	1087

Our outpatient care for people with diabetes mellitus is carried out together with our colleagues from the Department of General Internal Medicine. Dr. M.N. Kerstens is the coordinator for diabetes care. Since the beginning of September 2006, diabetes care is offered based on a 'One Stop' principle in the University Diabetes Center, the first dedicated Diabetes Center in the Northern part of The Netherlands, and the first Academic Center in our country. All care providers can be found within the same location, i.e. the first floor of the A-wing of the Triade building (entrance 23). Here a patient can be seen by the internist, diabetes nurse specialist, dietician, podotherapist. There is a facility for making retinal photographs, and for drawing blood for laboratory determinations. In the first quarter of 2009 we have also started clinics by a psychologist. In addition, one floor lower patients can participate in all kinds of sports activities in the Sports and Movement Center. 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.

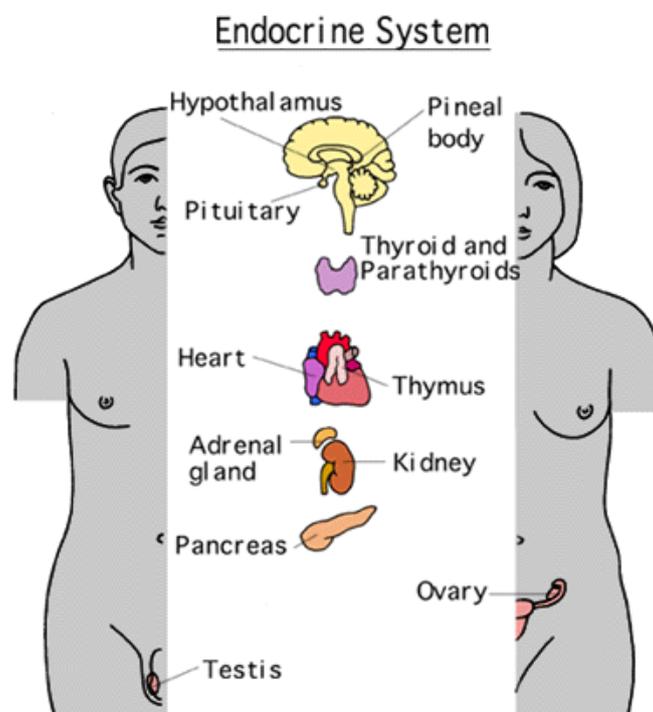


Figure 2. The Endocrine System

### **'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, pheochromocytoma, disturbances of steroid synthesis)
- \* endocrine tumour syndromes (MEN1, MEN2, VHL, neurofibromatosis etc)
- \* pregnancy in diabetes
- \* diabetic complications, including diabetic foot problems

\* insulin pump therapy.

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!

### **Experiences with Cushing's disease 1998-2009**

We report our experience in Cushing's disease over a period of 12 years (1998-2009), also on behalf of the other members of the Pituitary Working Group in our hospital. Thirty-nine patients underwent pituitary surgery, primary in 38 cases, and repeated surgery in one case, followed by secondary surgery in 4 patients and tertiary surgery in 2 patients. All surgery except for one was along the transsphenoidal route, presently using the endoscopic technique. In total, 47 operations were performed.

Remission was defined as the disappearance of clinical signs, presence of low levels of serum cortisol shortly after surgery, with the temporary need for (hydro)cortisone substitution, and afterwards a normalized 24 hrs urine free cortisol together with adequate suppression of serum cortisol after 1 mg dexamethasone overnight (<50 nmol/l).

The group consisted of 8 male and 31 female patients, representing 24 microadenomas, 6 macroadenomas, and 9 cases with occult disease. Inferior petrosal sinus sampling was performed in 8 of those 9 cases, confirming a pituitary origin. One microadenoma and one macroadenoma showed invasion of the cavernous sinus on MRI. The mean follow-up was 67 months (1-136).

Remission was achieved in 34 patients (87%). Recurrent disease developed in 4 patients, after a follow-up period of 8-38 months (11%). Repeated surgery was unsuccessful in recurrent disease. All 4 patients underwent stereotactic radiotherapy (45 Gy/25 fractions).

Primary failure was present in 5 patients, with remission after secondary surgery in 2 patients. A third patient was treated by radiotherapy, one patient died, and in a last patient subclinical disease was accepted until now. Overall repeated surgery was only successful in 3 out of 9. Occult disease was cured in 5 out of 9 cases.

Two patients died due to cerebrovascular disease, 9 years and 6 months after surgery, the latter with persistent Cushing's disease. A third patient died, while being in remission for 3 years, after a myocardial infarction. The overall mortality was 8%.

Stable remission is still present in 30 patients (76%), with a mean follow-up of 67 months (1-136).

Cushing's disease is a very rare disease, even in a center for tertiary care, and results in dramatic clinical consequences for the patients involved. Management of these patients should be centralized in a few highly specialized centers, with a documented proper success rate. The main focus should be on the improvement of the surgical cure rates.

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#### ***Multidisciplinary patient care***

We have multidisciplinary groups of physicians 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 Centre. 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.

Dr. Links is responsible for the Multidisciplinary Thyroid Team, dr. van den Berg and dr. van der Klauw for the Pituitary Outpatient Clinic, prof. Wolffenbuttel for the Diabetic Foot Collaboration and 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. Also there is intensive interaction with the Department of Oncology related to the treatment of patients with other endocrine tumours.

All these activities are not possible without the assistance of a dedicated staff of administrative personnel. These included in 2009 Monique Gelms, Anita Scholtens, Ada Schaaf, Berber Brandsma, Nihaila van den Berg-Sillé, Fenna Diepenbroek-Beulakker, Bea te Nijenhuis and Alie Tigelaar, as well as all the administrative personnel responsible for the letters to G.P.'s regarding our patients.

## **4a. Diabetes mellitus / Diabetes Care**

### **Integrated diabetes care**

The UMCG supports the concepts of the Dutch Diabetes Federation, which are summarized in a specific Standard of Care for the Treatment of Diabetes. 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, in the middle of the city of Groningen. The other location harbours the Diabetes Rehabilitation program, and is situated within the Centre for Rehabilitation Beatrijcoord. Together, these locations form the University Diabetes Center, the only Diabetes Knowledge and Expertise Center in the northern part of The Netherlands.



*Fig. 3. The Diabetes Center*

The diabetes nursing staff consisted of:

mrs. Els van Driesum, head nurse; mrs. Berber T. de Boer, Carla Janson, Immie Hoekstra, Alied Jongbloed, Susanne Pathuis and Roelie Zuur, diabetes nurse specialists; Winnie van El, nurse practitioner; Gillian Kreugel, Msc, nursing consultant.

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, 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 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 out-patient 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. Follow-up appointments with the endocrinologist and the diabetes nurse are planned. In some cases the teenager comes together with the parents. We have a special afternoon for the transition-group so they can meet each other in the waiting room. In 2008, 24 teenagers have made the transition to the out-patient clinic for adults. In 2009 this group was still seen separately, and in 2010 a new group will follow. 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.

#### *b. Pregnancy*

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

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

#### *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 nephrological 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).

#### 4. Group sessions

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



Fig. 4. Education materials at the outpatient clinic

#### 5. Psychological care

Psychological problems, such as depression, are a common comorbidity of diabetes. Rates range from 11% to 20%. Growing evidence from clinical studies indicates that the presence of comorbid depression in diabetes has several implications for physical and mental functioning. It is associated with lower

adherence to medication, dietary, and exercise recommendations and poorer physical performance and also with hyperglycemia. Given the high comorbidity of depression in diabetes and its potential negative impact, it is important to identify and treat patients with these problems. Therefore we conducted a screening- and intervention pilot in which we tested (1) an online screening program and (2) the acceptability and feasibility of a new type of cognitive therapy, namely Mindfulness Based Cognitive Therapy.

We approached 519 diabetes patients, of whom 348 (70%) completed the questionnaire. 244 (70.2%) of the respondents scored below the cut-off on the screening questionnaire, and 104 (29.8%) had elevated levels of psychological problems. All 104 patients with elevated scores received a phone call to invite them for a 1-hour diagnostic interview to gain further insight into their problems and discuss whether additional care is needed. 48 patients accepted this invitation, and 23 of them were included in the intervention study. 12 patients were treated immediately, 11 were treated after 3 months (waitinglist-control design). All patients were asked to complete questionnaires at 3 time points. Data are currently being collected, we hope to start analyzing from July 2010 onwards.

Project leaders : Joke Fleer PhD, Joost C. Keers PhD, Thera Links MD PhD, Bruce Wolffenbuttel MD PhD, Robbert Sanderman PhD, , University Medical Center Groningen, University of Groningen, the Netherlands

## **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, sometimes referred to as a 'diabetes carousel', 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 Centre come from all around The Netherlands, even from the southern provinces of Limburg and Brabant. However, the majority of them live in one of the four (or five if you include Flevoland) northern provinces: Groningen, Friesland, Drenthe or Overijssel. Their treatment is based on formalized treatment protocols, which include the majority of advices and guidelines issued by the Dutch Diabetes Federation. Our clinical care would be very much facilitated when we would have the availability of an Electronic Patient File.

## **7. Diabetes Rehabilitation**

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

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

Long term results of the program are excellent, as described by our psychologist Joost Keers, who defended his thesis on this topic in 2005. Permanent improvement of diabetes control as well as health-related quality of life, but above all improved self-management skills have been the most

important achievements. For this reason, the Association of Rehabilitation Physicians and the Dutch Diabetes Federation have rated this program 'a high quality and indispensable asset'. After long negotiations with governmental bodies, we received in 2007 official approval of this program, and subsequently a considerable coverage of the program by health care insurance companies.

The following people form the team responsible for the Diabetes Rehabilitation Program (figure 5): Mrs. Rita Wesselius, team coordinator; Mrs. Linda Faber, Mrs. Ingrid Stoelinga, Mrs. Madelein Schotman, diabetes nurse specialists; Mrs. Marianne van Dijk, dietician; Mrs. Brigitta Joosen, en Mrs. Renske Bouman, physiotherapists; Mr. Guus van Bochove, movement scientist; Mrs. Heike Mesch, psychologist; Mrs. Tilly Söder and Mrs. Jannet Waijer, social welfare; Mrs. Franka Waterschoot, ergotherapist.

They are supported by Mrs. Janine Kramer and Mrs. Elsa Pieterman-Slagter, secretaries; Mrs. Hennie Meijer, assistant.



*Fig. 5. The team of the Diabetes Rehabilitation program*

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. Diabetes care for patients admitted to other wards within the Rehabilitation Centre is supported by the endocrinologist and the diabetes nurse specialists.

## **8. Obesity**

An obesity rehabilitation program, which started in 2005, is available for patients with diabetes or metabolic syndrome and complicated obesity. 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 future development of an obesity treatment centre.

## 9. The podotherapist

A Diabetes center can not exist without dedicated people looking after the feet of our patients. We are lucky to have Marten de Haas as our podotherapist (figure 6), a young and eager care provider who is always prepared to devote extra time to his patients.



*Fig. 6. Please knock. Entry to the office of the podotherapist*

## 4b. General Endocrinology

### New developments

Turner's syndrome is a genetic anomaly that results from complete or partial absence of one X chromosome and is the most frequently occurring chromosomal abnormality in females. Adults with Turner's syndrome have an increased risk of developing multiple co-morbidities such as cardiovascular diseases, hypothyroidism, diabetes mellitus, osteoporosis, gastrointestinal disorders, hearing loss and the attendant problems of estrogen deficiency and infertility. Therefore, a multidisciplinary approach is needed for early detection and adequate treatment of the various problems that may affect adult women with this syndrome.

In September 2006, a specialized outpatient clinic for patients with Turner's syndrome has been started by the departments of Endocrinology and Gynaecology. In agreement with clinical guidelines that have been issued in recent years, patients visit this facility once a year and are examined at each visit by both the endocrinologist and the gynaecologist. The team is also staffed by social workers experienced with the specific psychosocial problems that Turner patients may be facing. In addition, patients are referred to the Cardiologist and Ear, Nose & Throat specialist for periodic evaluation once every 3 years, or more frequently if indicated. At present, the Turner outpatient-clinic is open to other patients from the northern region.

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

Several innovative PET methods have been used such as 18F-DOPA and 11C-5-HTP for imaging of medullary thyroid cancer, pheochromocytoma, carcinoids and pancreatic neuroendocrine tumours and 124I and 11C-methionin for papillary and follicular thyroid cancer. Ongoing research supports these developments in better staging of disease and applying new therapies. The Endocrinology department has participated in several national and international clinical trials with new targeted drugs like imatinib and vandetanib in patients with medullary thyroid cancer. In the spring of 2009 participation in a international multicenter trial with the multikinase inhibitor XL184 for medullary thyroid cancer will start.

In February 2009 a national project for screening of pancreatic neuroendocrine tumours in Multiple Endocrine Neoplasia type 1 and Von Hippel-Lindau disease has started employing imaging with endoscopic ultrasound and 11C-5-HTP PET. This project is supported by the Dutch Cancer Society. Aim of the study is to define the value of [11C]-5-HTP-PET and EUS compared to CT/MR and octreotide (conventional imaging) in patients with MEN1 and VHL with proven pancreatic neuroendocrine tumor involvement or in screenings setting. For this study, two groups are defined Group A (N=40): patients with already presence of neuro-endocrine tumors at CT/MRI scan and/or octreotide scan and/or biochemically proven and Group B (N=50): patients with no signs of pancreatic neuroendocrine tumors. In cooperation with University Medical Hospitals of Utrecht, Rotterdam and Nijmegen in 2000 24 patients were included. Recruitment of patients is at our attention. The VHL Family Alliance from the USA has supported an imaging study for visualizing VEGF producing lesions in Von Hippel-Lindau disease. This project has been started at the end of 2009 and is still recruiting patients.

For the diagnostics of catecholamine excess a rapid sensitive and highly selective automated method for plasma free metanephrine and normetanephrine is available on the Department of Clinical Chemistry (prof. dr. I.P. Kema). This quick method enables the routine quantification of catecholamines and their metabolites for daily patient care, but also creates possibilities to perform more in-depth analyses of the biochemical activities of neuroendocrine tumours.

The 18F-DOPA PET scanning has been evaluated and shown to be superior to conventional imaging in localizing tumors causing catecholamine excess.

In close collaboration with the Leiden University Medical Center (prof dr J.W.A. Smit and Dr. H.W.Kapiteijn) several studies regarding differentiated thyroid cancer are in preparation and will be started in the spring of 2010

***National I-131 Remnant Ablation study in patients with Differentiated Thyroid Cancer -optimal treatment with maximal outcome-***

*Rationale of the study*

*Patients with differentiated thyroid cancer (papillary and follicular) are treated with near-total thyroidectomy. In most of the patients this treatment has to be followed by ablation with I-131 to eliminate remnant thyroid tissue to decrease the risk of tumor recurrence and improve sensitivity and specificity of Tg measurement in follow-up. With the introduction of rhTSH the question arises, whether ablative therapy after pretreatment with rhTSH during euthyroidism can be used instead of the classical way of inducing hypothyroidism by withholding suppletion which induces endogenous rise of the TSH level. Objectives To determine the rate of ablation failure in differentiated thyroid cancer patients using rhTSH instead of thyroid hormone withdrawal for stimulation of remnant tissue, using a fixed dosage of 3.7 GBq (100 mCi).*

*Study design*

*Prospective multicenter study in the Netherlands.*

*Study population*

*The maximum number of patients will be 144.*

*Intervention (if applicable)*

*Two rhTSH injections will be given 6 weeks after total thyroidectomy (before I-131 treatment) and 9 months after the first high dosage I-131 treatment.*

*Main study parameters/endpoints:*

*The primary endpoint of successful ablation is defined as: rhTSH Tg < 1ng/ml, negative rhTSH dxWBS, negative neck US and negative Tg antibodies*

*The study will start in the spring of 2010, and be performed in close cooperation with Nijmegen Medical Center, Leiden University Medical Center, Maastricht University Medical Center, University Medical Center Utrecht, Academic Medical Center Amsterdam, Meander Medical Center Amersfoort, and VU Medical Center Amsterdam  
Financial support was obtained by Genzyme*

Primary aldosteronism 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 aldosteronism 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 aldosteronism, and is currently one of the main referral centres in the Netherlands for adrenal venous sampling. Personal experience of the radiologists with adrenal venous sampling and application of rapid cortisol measurements during the procedure have resulted in a success rate of about 85 %

We received sponsoring from the UMCG for conducting a pilot study in which we will examine the diagnostic value of <sup>11</sup>C-metomidate-PET/CT to differentiate between bilateral adrenal hyperplasia and aldosterone producing adenoma. Inclusion of the first participants is scheduled for 2010.

## 5. Teaching

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

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

Dr. Dullaart has been appointed coordinator for Year 2 of the International Bachelor program. The Groningen Medical School offers a modern multidisciplinary curriculum in which problem-based learning principles are applied in a patient-centred context. During the Bachelor's programme, students first become familiar with basic medical disciplines such as anatomy, biochemistry, physiology and neurosciences. In the second and third years, the focus is on clusters of related diseases or conditions. In the international Bachelor's profile, special attention is paid to different aspects of global health, such as emerging diseases, different health-care systems and nutrition and health. During the Bachelor's phase all students will have to learn Dutch to facilitate communication with patients.

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).

On January 13, prof. Wolffenbuttel gave a presentation on new development in type 1 diabetes during the 'Year in Endocrinology' symposium, and on January 22 during the symposium on Diabetes and Kidney Diseases. In February he gave a presentation during the Expert Meeting on Innovations in Diabetes Care which was organized by the Dutch Diabetes Federation.

On Saturday January 31, a meeting was held for Turner patients. This was highly successful and more than 200 patients and family participated in this mini-conference to hear about new developments in the care for Turner patients. Medical specialist gave an update on chromosomes, growth and puberty, and healthy life style in adulthood,. In addition, there was also attention for pregnancies, psychological aspects and the Turner patient association (Turner Contact Nederland). Dr. M.N. Kerstens and Dr. A.P. van Beek participated as endocrinologist in this multidisciplinary field of specialists.

On April 23, dr Kerstens held a presentation at the annual meeting of the Dutch Society for Internal Medicine ('Internistendagen') entitled 'Cushing's syndrome as a model for cardiovascular disease'.

On May 8 the department participated in the very successful Alpha-Omega congress on continuous glucose monitoring.

On October 15, the department participated in the yearly Endocrinology Teaching Evening which is specially organised for General Practitioners. Title of the evening was 'Super size me'. Drs. H. Mesch, Dr. A.N.A. van der Horst, Dr. A.P. van Beek and Prof. Dr. B.H.R. Wolffenbuttel informed general practitioners and their assistants on psychological and medical aspects in the treatment of patients with obesity and diabetes mellitus.

Finally, during the yearly Erasmus Postgraduate Course on Endocrinology in Noordwijkerhout, dr. Melanie van der Klauw and prof. Wolffenbuttel gave a workshop titled 'Treatment of diabetes and severe insulin resistance'. Due to the high number of participants this workshop had to be repeated twice during the course of the meeting.

### *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, a 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. For more information see [www.diabetes.nl](http://www.diabetes.nl). Since 2009 Dr. André van Beek is the chief editor of this journal as successor of prof. B.H.R. Wolffenbuttel who held this job since the start of the journal in 2003.



### *Digidiabetes*

Another form of collaboration with Pronounce and the Postgraduate Education Institute (Wenckebach Institute) of the UMCG resulted in an e-learning program for nurses. The E-learning program for nurses was updated in 2008. By use of this program, nurses working in hospitals but also pharmacy assistants and other health care providers can learn the latest information on diabetes mellitus, its pathophysiology and treatment, with this diabetes training program, according to the blended learning possibilities. This approach uses an electronic education program (Digidiabetes) followed by a practical training, given by a diabetes nurse specialist.

### *Teaching Course for Diabetes Nurse Specialists*

In October 2009, the Second 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

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

At present, dr. R.P.F. Dullaart coordinates the Endocrinology teaching program. All staff members contribute to the training program. In 2009 two MD's, Mrs. Helen Lutgers and Mrs. Adrienne Persoon (as of February 2010) followed the Endocrinology training program.

In April 2009 two regional study days incorporated in the Internal Medicine training program have been organized by Prof. Dr. Wolffenbuttel. The topic of this day was 'Endocrinology', with an emphasis on thyroid, adrenal diseases and calcium homeostasis.

## 8. Scientific research

The research of the Department of Endocrinology is part of the Kidney Centre and the Cardiovascular Centre 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: Innovative strategies in *differentiated thyroid cancer*  
researcher: mrs. A.C.M. Persoon  
supervisor: dr. T.P. Links, prof. dr. P.L. Jager  
promotor: prof. dr. B.H.R. Wolffenbuttel  
thesis: March 2009

topic: *Medullary thyroid cancer: distinction and treatment of progressive disease*  
researcher : H.H.G. Verbeek  
supervisor : prof. dr. T.P. Links,  
promotor prof. dr. R.M..W. Hofstra, prof. dr. J.T.M. Plukker  
thesis: 2012

topic *Prognostic factors in differentiated thyroid cancer*  
researcher D. Van Dijk  
supervisor prof. dr J.T.M.Plukker, prof. dr T.P.Links  
thesis 2013

topic: *Hürthle cell carcinoma and RET/PTC rearrangements*  
researcher: mrs. M. de Vries  
supervisor: prof. dr. R.M.W. Hofstra, prof. dr. T.P. Links

topic: *Vascular effects in thyroid cancer patients*  
researcher B.Groen  
supervisor prof. dr T.P.Links, dr. J. Lefrandt, dr. A.N.A. vd Horst-Schrivers

##### 2. Pituitary tumors

topic: *Long-term effects and quality of life after treatment for pituitary adenoma and Cushing's disease*  
researcher: drs. M. Sattler (radiotherapist)  
supervisor: dr. A.P. van Beek, dr. A.C.M. van den Bergh  
promotor: prof. dr. J.A. Langendijk, prof. dr. B.H.R. Wolffenbuttel  
thesis: 2011

topic: *Cognitive functioning in patients with pituitary adenoma*  
researcher: drs. P. Brummelman (psychologist)  
supervisor: dr. A.P. van Beek,  
promotor: prof. dr. B.H.R. Wolffenbuttel  
thesis: 2012

### **3. Neuro-endocrine tumours**

topic: *Imaging in neuroendocrine tumours*  
researcher : ms. H.B. Fiebrich  
supervisor: dr. A.H. Brouwers, prof. dr. T.P.Links  
promotor: prof. dr. T.P. Links, prof. dr. E.G.E. de Vries  
thesis: 2010

topic: *Disease activity in MEN 1 and VHL*  
researcher: ms. S.van Asselt  
supervisor: dr. A.H. Brouwers, prof. dr. T.P.Links  
promotor: prof. dr. T.P. Links, prof. dr. E.G.E. de Vries  
thesis: 2013

Topic *The role of chemokines and angiogenesis in the development of metastasases and the possible treatment in Von Hippel Lindau Tumours*  
Researcher ms. R. Kruizinga  
Supervisor/ prof. dr. E.G.E. de Vries, prof. dr. T.P. Links, dr. A.M.E. Walenkamp,  
Promotor  
Thesis 2013

topic: *Diagnosis and treatment of catecholamine secreting neuroendocrine tumors*  
researcher: ms. T.E. Osinga  
supervisor: dr. A.N.A van der Horst-Schrivers, dr M,N, Kerstens, dr R.P.F. Dullaart  
promotor: prof. dr. T.P. Links, Prof .dr.I.P.Kema  
thesis: 2014

## **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*
- d. *Etiology and treatment of type 1 diabetes*
- e. *Genetic predisposition for type 2 diabetes*
- f. *Gene-environment interaction in the development of type 2 diabetes*

topic: *Towards a personalized risk assessment and therapeutical strategy to prevent and treat macrovascular disease in Type 2 diabetes*  
researcher: J. van Ark  
promotor: prof. Dr. J.L. Hillebrands, prof. dr. B.H.R. Wolffenbuttel

co-promotor: dr. J. Moser, dr. H. van Goor  
thesis: 2012  
support: Diabetes Research Foundation (DFN)

topic: Skin autofluorescence in the dark skin  
researcher: Marten Koetsier  
promotor: Prof dr G Rakhorst, prof dr T.P.Links  
co promotor: dr A.J.Smit, dr R. Graaff, dr.H.L.Lutgers  
thesis 2010

## **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.*

*In 2006 the NFU submitted a proposal for a project to build a joint infrastructure to collect and access the patient data and biomaterials of at least eight patient categories. In the coming years each of the eight UMC's will take the initiative to build a joint database and biobank for all patients with a specific diagnosis using uniform definitions and storage circumstances. The following patient cohorts are planned: Inflammatory Bowel Disease, Rheumatoid Arthritis, CVA, hereditary Bowel cancer, Leukemia, Dementia, Diabetes.*

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

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

*For more information: [www.parelsnoer.org](http://www.parelsnoer.org)*

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.

This research programs are carried out by the Department of Endocrinology (dr. R.P.F. Dullaart, dr. T.P. Links, prof. dr. B.H.R. Wolffenbuttel) in close collaboration with the Dept's of General Internal Medicine and Nephrology: Dr. S.J.L. Bakker, dr. A.J. Smit, prof. dr. R.O.B. Gans, and with dr. A. van Tol, Department of Cell Biology and Genetics, and mrs. dr. G. Dallinga - Thie, Department of Internal Medicine, both of the Erasmus Medical Centre Rotterdam.

## **2. Metabolism, obesity and metabolic syndrome**

topic: *Thyroid (dys)function, metabolic syndrome and incident cardiovascular disease*  
researcher: A. Roos  
promotor: prof. dr. B.H.R. Wolffenbuttel, prof. dr. T.P. Links  
co-promotor: dr. A. Berghout (internist, Rotterdam), dr. S.J.L. Bakker (internist)  
thesis: 2011

topic: *The role of a lifestyle program and fat distribution in women with obesity and infertility*  
researcher: W.K.H. Kuchenbecker, gynaecologist  
supervisor: dr. A. Hoek, dr. H. Groen  
promotor: prof. dr. J.A. Land, prof. dr. B.H.R. Wolffenbuttel  
thesis: 2011

topic: *Metabolic aspects of body fat, reproduction and intervention*  
researcher: mrs. J.G. Dolfing, gynaecologist  
supervisor: dr. D.H. Schweitzer (internist, Voorburg)  
promotor: prof. dr. B.H.R. Wolffenbuttel  
thesis: 2011

topic: *The healthy obese; does it exist and matter for prognosis?*  
researcher: F.A.J. Verburg  
promotor: prof. dr. B.H.R. Wolffenbuttel  
co-promotor: dr. A.P. van Beek  
thesis: 2011

## **3. Diabetes psychology and quality of care**

topic: *Diabetes education: effects of self-adopted therapy goals and partner behaviour*  
researcher: mrs. M. Schokker  
supervisor: prof. dr. T.P. Links, dr. J. Bouma, dr. J.C. Keers  
promotor: prof. dr. M. Hagedoorn, prof. dr. R. Sanderman, prof. dr. B.H.R. Wolffenbuttel  
thesis: September 2010

topic: *What helps patients to keep their medication plan? Compliance vs self-management.*  
researcher: mrs. R. Visser  
supervisors: dr. J.C. Keers, dr. P. Denig

topic: *GIANTT: assessing pharmacotherapeutic care for patients with type 2 diabetes*  
researcher: J. Voorham  
promotor: prof. dr. F. Haaijer-Ruskamp, prof. dr. B.H.R. Wolffenbuttel  
co-promotor: dr. P. Denig  
thesis: June 2010

topic: *'Diabetes VerjaarDAG': Implementation of yearly counselling by a diabetes nurse specialist*  
researcher: G.Kreugel  
supervisor: prof. dr. B.H.R. Wolffenbuttel

topic: *Care improvement for diabetic patients with chronic renal failure (CRF)*  
researcher: W. van El  
supervisor: dr. C.F.M. Franssen (nephrologist), dr. J.C. Keers, dr. M.N. Kerstens, prof. dr. T.P. Links

topic: *INOBESE, The influence of the needle length on long term glycaemic control in insulin using obese diabetic subjects*

researcher: G. Kreugel  
supervisor: prof. dr. B.H.R. Wolffenbuttel

Mrs. G. Kreugel has presented her results in a special poster session at the American Diabetes Association (ADA). June 5-9, 2009 in New Orleans.

### **Program III. General endocrinology**

#### **1. Thyroid**

topic: *Amiodarone effects and side effects*  
researcher: S. Ahmed  
supervisor: prof. dr. T.P. Links  
promotor: prof. dr. I.C.van Gelder, prof. dr. D.J. van Veldhuizen  
thesis: 2010

topic: *Primary hypothyroidism in the general population*  
researcher: ms. E.I. Klaver  
supervisor: dr. M.M. van der Klauw  
promotor: prof. dr. B.H.R. Wolffenbuttel  
thesis: 2012

topic: *Use of the RFFT as a measure of cognitive function in endocrine disease*  
researcher: M. Elderson  
promotor: prof. dr. B.H.R. Wolffenbuttel, prof. dr. J. Slaets  
thesis: 2012

## **Participation in (inter)national clinical trials**

### **DURABLE:**

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

### **4B:**

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

### **LOWER:**

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

### **METOPET:**

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

### **GALAHAD**

Evaluating the relationship between haemodialysis and glucose control in insulin-treated diabetic patients – a pilot study (NL32332)

### **ARRAT:**

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

### **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:

### **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:

### **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:



### **LifeLines**

*The risk to develop multifactorial diseases is determined by risk factors that frequently apply across disorders (universal risk factors). To investigate presently unresolved issues on etiology of and individual's susceptibility to multifactorial diseases, research focus should shift from single determinant–outcome relations to effect modification of universal risk factors.*

*A study to assess disease risk during life requires phenotype and outcome measurements in multiple generations with a long-term follow up. The latter will also enable to separate genetic and environmental factors. Traditionally, representative individuals (proband) and their first-degree relatives have been included in this type of research. A three-generation design is an improved approach to investigate multifactorial diseases. This design has statistical advantages (power and precision, multiple informants, separation of non-genetic and genetic familial transmission, direct haplotype assessment, quantify genetic effects), enables unique possibilities to study social characteristics (socioeconomic mobility, partner preferences, between-generation similarities), and offers practical benefits (efficiency, lower non-response).*

### **Concepts**

*LifeLines is a cohort study to investigate universal risk factors and their modifiers for multifactorial diseases. It will help to better understand the causes and prognosis of burden of chronic diseases over lifetime and may ultimately result in optimal tailored treatment of individual diseases and disease overriding preventive strategies. Specific research questions will focus on risk factors and modifiers (genetic, environmental and complex factors) for single and multiple diseases. Rather than co-morbidity, LifeLines focuses on co-determinants. Secondary aims include the assessment of the prevalence and incidence of multifactorial diseases and their risk factors in individuals as well as in families. The burden of disease for the society will be quantified in terms of care needed.*

*LifeLines is an observational follow-up study in a large representative sample of the population of the northern provinces of the Netherlands covering three generations. Firstly, a random sample of persons aged between 25 and 50 years are invited to participate. Subsequently these probands invite their family members to take part as well (parents, partner, parents in law, children), resulting in a three-generation study including 165.000 participants: 45.000 probands, 30.000 partners, 55.000 parents (in law) and 35.000 children.*

*The core of the LifeLines project consists of dedicated data collection and biological sample storage, including genetic samples ("biobank"). All participants receive a number of questionnaires and a basic medical examination and are followed for many years with extensive standardized measurements.*

*Methods of data collection are matched with other ongoing biobank studies (P3G consortium), which enables combining datasets to construct large study populations. LifeLines participates in the BBMRI consortium ([www.bbMRI.eu](http://www.bbMRI.eu)).*

*For more information readers are referred to the website [www.lifelines.nl](http://www.lifelines.nl).*

## **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 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).

Dr. Links is advisor of the foundation "BETER", that 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](http://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.

Prof. dr. 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 Centre 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. dr. B.H.R. Wolffenbuttel is member of the Board of the journals International Diabetes Monitor and International Growth Monitor, as well as Expert Opinion in Pharmacotherapy. He was until the fall of 2009 member of the ZonMW Committee on Prevention. He also serves as secretary of the Dutch Endocrine Society.

Dr. J.C. Keers is member of the Committee on Education and Publicity of the Dutch Diabetes Federation.

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 serves 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)

## **Addendum 1 - Conferences**

Endocrinology Grand Rounds	weekly (Tuesday 9.00 - 10.30)
Endocrine Case Conference	weekly (Friday 9.00 - 10.00)
Internal Medicine Patient Discussion	every two weeks (Tuesday 16.45 - 17.30)
Thyroid Carcinoma Consultation	monthly (Friday 11.00 - 12.30)
Diabetic Foot Rounds	weekly clinical rounds (Monday) 1x monthly (Friday)
Pituitary Case Conference	every two weeks (Tuesday 12.00 – 13.00)
Multidisciplinary Diabetes Consultation	once monthly (Thursday, 16.30 - 17.30)
Endocrine Pathology Case Conference	once every 2 months (Friday 9.00 - 10.00)
Vascular Medicine Research meeting	every two weeks (Tuesday 16.45 -17.30)
Endocrinology Journal Club	monthly (Friday 9.00 - 10.30)
Regional Case and Research Conferences	6-8 times a year

## **Addendum 2 - Multidisciplinary teams**

### **Thyroid**

Prof. dr. T.P. Links, Dr. A.N.A. van der Horst-Schrivers, Endocrinology  
Prof. dr. J.T.M. Plukker, dr. L. Jansen, Oncologic Surgery  
Dr. A. Brouwer and colleagues, Nuclear Medicine  
Dr. F. Burlage, Radiotherapy  
Dr. P. C. Jutte, Orthopedics  
Dr. M. Coppes, Neurosurgery  
Dr. A. Muller Kobold, Clinical Chemistry  
Staff members of Endocrinology

### **Pituitary**

Dr. G. van den Berg, Endocrinology  
Dr. M.M. van der Klauw, Endocrinology  
Dr. E. Hoving, 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. Dr. PP van den Berg, Obstetrics/ Gynaecology  
Prof. dr. T.P. Links, Endocrinology  
Dr. K.M. Sollie, Obstetrics/ Gynaecology  
Dr. F.A.J. Verburg, Endocrinology

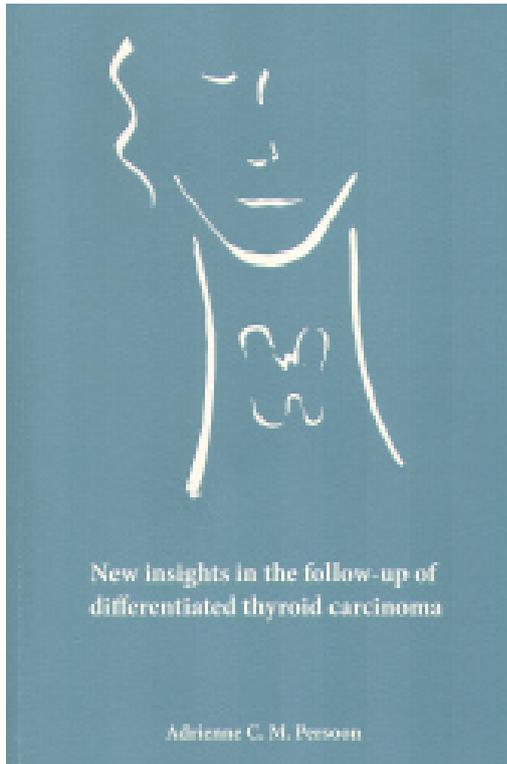
### **Turner team**

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 2009

### PhD Thesis / dissertations

**A.C.M. Persoon: "New insights in the follow-up of differentiated thyroid carcinoma;  
March 4, 2009**



Promotores: **Prof. dr. B.H.R. Wolffenbuttel**, Prof.dr. P.L. Jager

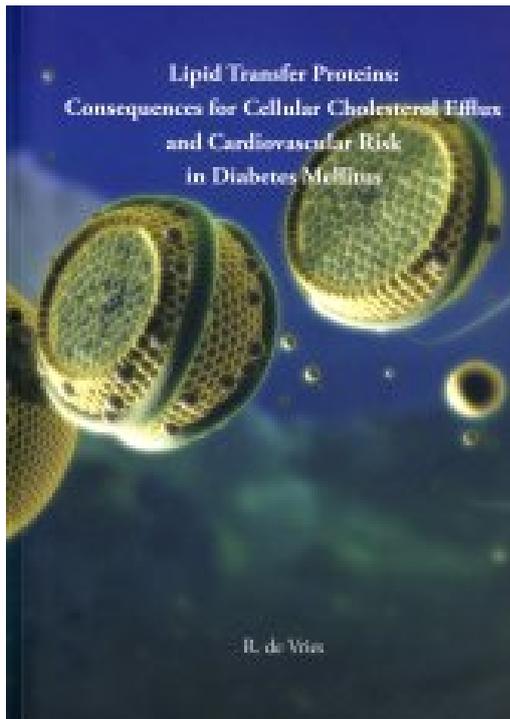
Co-promotores: **dr. T.P. Links, dr. W.J. Sluiter**

Summary:

Generally, differentiated thyroid cancer (DTC), including papillary and follicular thyroid cancer, carries an excellent prognosis. Ten-year survival rates range between 83% and 98%. This favorable prognosis results from both the effective initial therapy and the generally indolent biological behavior of this tumor. Initial therapy consists of total thyroidectomy followed by high dose radioiodine therapy to eliminate microscopic residual or metastatic disease and subsequent lifelong thyroid hormone supplementation therapy. Despite the favorable general prognosis, recurrence rates are high, as up to 20% develop recurrent disease during follow-up. Recurrences may become clinically evident even after 20 years following this initial therapy. Therefore lifelong follow-up of thyroid cancer patients is recommended. Follow-up strategies should be able to identify patients with recurrent disease. However, a proper

balance between the diagnostic yield of monitoring tests and the associated patient burden and medical costs should be maintained.

**R. de Vries: “Lipid transfer proteins: consequences for cellular cholesterol efflux and cardiovascular risk in diabetes mellitus”; February 11, 2009**



This thesis studies the changes in the ability of plasma to stimulate cellular cholesterol efflux in type 1 and type 2 diabetes mellitus and the alterations in lipid metabolism mediated by lipid transfer proteins and its risk of cardiovascular disease in type 2 diabetes mellitus. Efflux to plasma from moderately hypercholesterolaemic type 1 diabetes patients is enhanced, probably due to an increased apo A-I, HDL phospholipids and PLTP activity. Simvastatin increases HDL cholesterol via lowering of plasma cholesteryl ester transfer. The HDL changes after simvastatin do not increase cellular cholesterol further. Reduction in dietary saturated fat and cholesterol intake does not adversely affect cellular cholesterol efflux to plasma from type 1 diabetic patients, despite a drop in pre  $\beta$ -HDL formation. Efflux to hypertriglyceridaemic diabetic plasma is enhanced, in association with increased plasma PLTP activity and cholesterol esterification. Unaltered pre  $\beta$ -HDL formation in diabetic hypertriglyceridaemia, despite low apo A-I, could contribute to maintenance of cellular cholesterol efflux.

Plasma CET is a positive determinant of IMT in type 2 diabetes mellitus and control subjects. Plasma CETP mass, in turn, is a determinant of CET with an increasing effect at higher triglycerides. Plasma PLTP activity is a positive determinant of IMT in type 2 diabetes mellitus, suggesting that high PLTP activity is involved in accelerated atherosclerosis in this disease.

Specific CETP activity is decreased in type 2 diabetes mellitus. Specific PLTP activity is higher in diabetes, as a result of the association of plasma PLTP activity with plasma triglycerides and obesity.

## Publications international

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Fiebrich HB, Brouwers AH, **Kerstens MN**, Pijl MEJ, Kema IP, de Jong JR, Jager PL, Elsinga PH, Dierckx RAJ, van der Wal JE, **Sluiiter WJ**, de Vries EGE, **Links TP**. 6-[F-18]Fluoro-L-Dihydroxyphenylalanine positron emission tomography is superior to conventional imaging with <sup>123</sup>I-metaiodobenzylguanidine scintigraphy, computer tomography, and magnetic resonance imaging in localizing tumors causing catecholamine excess. J Clin. Endocrinol Metab 2009; 94: 3922-30

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proteinuric patients: relationships with cholesteryl ester transfer protein mass and adiponection. *Expert Opinion Ther Targets* 2009; 13: 497-504

**Lutgers HL**, Gerrits EG, **Sluiter WJ**, Ubink-Veltmaat LJ, Landman GWD, **Links TP**, Gans ROB, Smit AJ, Bilo HJG. Life expectancy in a large cohort of type 2 diabetes patients treated in primary care (zodiac-10). *PlosOne* 2009; 4: e6817

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

