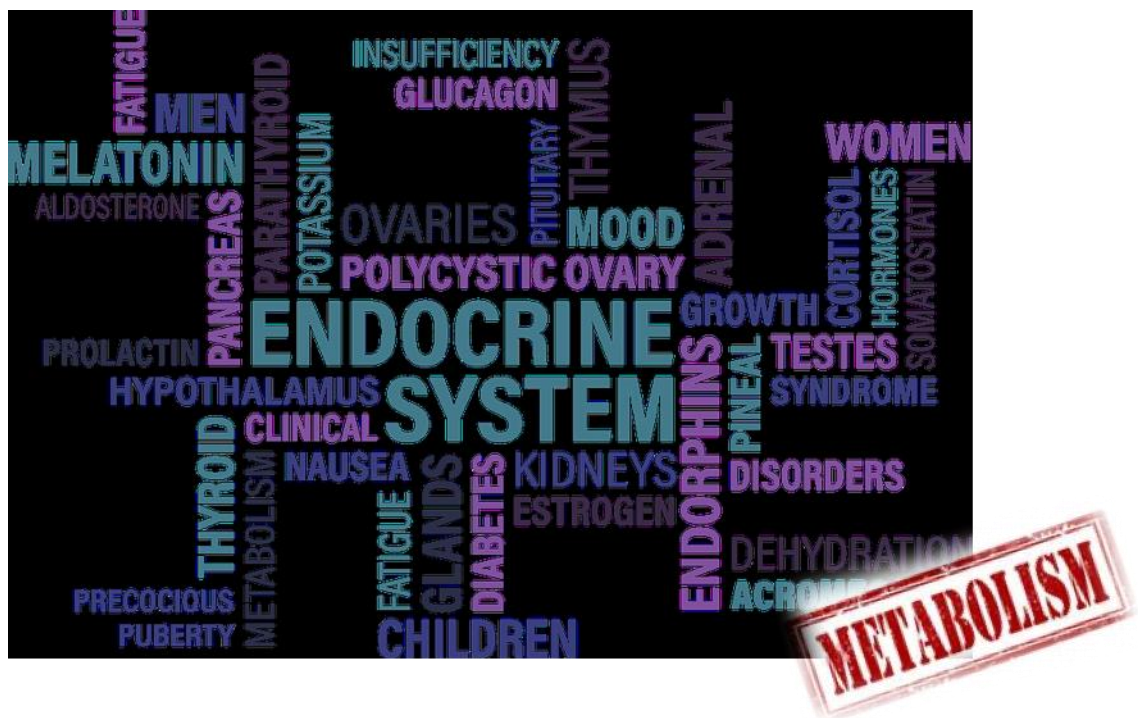




5th JNVE conference

October 25 and 26 2018 Nijmegen



This meeting is kindly sponsored by the Dutch Endocrine Society (NVE).



JNVE meeting 2018

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Introduction

Dear colleagues,

Welcome at the fifth conference of the Jonge Nederlandse Vereniging voor Endocrinologie (JNVE). We, as JNVE board, hope to provide you with an inspiring and interactive conference with lectures of well-known national invited speakers, a talented international speaker from Germany and presentations of 27 young endocrine researchers and clinicians from all over the Netherlands.

The JNVE was founded in March 2014 by eight young endocrine researchers and clinicians and is part of the Dutch Endocrine Society (Nederlandse Vereniging voor Endocrinologie (NVE)). We aim to provide a highly interactive platform for those that are at an early stage in their career related to the field of endocrinology. This includes everyone with a general interest in endocrinology including students, researchers (PhD students and postdocs) and medical doctors in training for internist, pediatrician, obstetrician as well as clinical chemists. The JNVE conference is aiming to promote interaction and communication between young basic researchers and clinicians and to provide many of you the opportunity to discuss their recent research data in an interactive and open atmosphere.

The JNVE is part of a group of similar initiatives for young endocrine professionals all over Europe. The very beginning of the initiative to unite young endocrinologists lies back in the 1990s, when the German Young and Active Research in Endocrinology (YARE) group was founded by Wiebke Arlt. She and her colleagues aimed to unite young endocrinologists of all kind and provide them a chance to interact with young colleagues and to present their work at an annual conference. In the subsequent years several other initiatives of young endocrine professionals have emerged all over Europe: YARE in Germany, ENGIOI in Italy, Klub 30 in Poland, FYEN in Denmark, the Young Endocrinologists in the United Kingdom and now the JNVE in the Netherlands.

These national initiatives are united in the European Young Endocrine Scientists (EYES) as a part of the European Society of Endocrinology (ESE), which is a vibrant group of young endocrine researchers and clinicians from all over Europe. EYES has its own symposium at the annual European Congress on Endocrinology as well as an own conference every year. From next year on, the JNVE will hand out a **scholarship** for one of the JNVE members to attend the EYES conference!

We are happy that as many of you are willing to participate in this 2018 JNVE meeting and hope that you will enjoy being part of the vibrant world of young endocrine professionals. Hopefully many of you will stay with us for a couple of years, until we have to admit that we are all getting too old for the JNVE and a new generation of young endocrinologists will take over the JNVE torch.

The JNVE-board

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Program JNVE meeting 2018

Day 1: Thursday 25th October 2018

- 12.00 **Registration and check-in van der Valk hotel Nijmegen-Lent**
- 12.00 **Lunch**
- 13.00 **Opening and Introduction**
Mariëtte Boon (Chair JNVE)
- 13.15 **Delegate session 1: Diabetes session: “Sweet siphon”**
- 14.15 **Invited lecture 1: The missing link – how epigenetics contributes to the development of obesity and type 2 diabetes**
Dr. Henriette Kirchner (University of Lübeck)
- 154.00 **Delegate session 2: GR receptor session: “Portmanteau (glucose + cortex + steroid)”**
- 16.00 **Tea and coffee break**
- 16.15 **Invited lecture 2: Would the brain be a target for diabetes treatment?**
Prof. Dr. Susanne la Fleur (Amsterdam UMC)
- 17.00 **Interactive seminar: Academic careers: successful talent selection or a race to the bottom?**
Dr. Marijtje Jongsma (Radboud UMC)
- 17.45 **Drinks at the bar**
- 18.30 **Dinner**
- 20.00 **Social evening program with pub quiz and party**

Delegate Session 1:

Diabetes session: "Sweet siphon"

Chairs: Mariëtte Boon and Anouk van Berkel

1. Early detection of hypoglycemia in type 1 diabetes using a wearable device measuring heart rate variability

Marleen Olde Bekkink (Radboud UMC)

2. Serum metabolites associated with fasting and postprandial measures of glucose metabolism in a non-diabetic population

Maxime M. Bos (LUMC)

3. C-peptide response to multiple stimuli in long-standing type 1a diabetes

Bas Uitbeijerse (LUMC)

4. Pasireotide LAR treatment in an dopamine-resistant and aggressive prolactinoma with excellent response

Sebastiaan van Meyel (Erasmus MC)

Delegate Session 2:

GR receptor session: “Portmanteau (glucose + cortex + steroid)”

Chairs: Mariska Vlot and Thamara Osinga

5. Differential co-regulator recruitment by glucocorticoid receptor modulators and effects on memory consolidation

Eva Viho (LUMC)

6. Glucocorticoid receptor-regulated transcription in metabolic tissues is modulated by androgen receptor signalling

Jan Kroon (LUMC)

7. A short-list of GR and CREB targets implicated in glucocorticoid-enhanced memory consolidation in the male rat brain

Rob J.C. Buurstedde (LUMC)

8. The effects of dexamethasone on glucocorticoid and mineralocorticoid receptors in human pediatric hippocampus

Anne-Sophie C.A.M. Koning (LUMC)

Program JNVE meeting 2018

Day 2: Friday 26th October 2018

- 08.45 **Delegate Session 3: Bone session: “I found this rather humerus”**
- 09.30 **Delegate Session 4: (Para)Thyroid session: “It's a (para)thyroid thing?”**
- 10.15 **Tea and Coffee break**
- 10.30 **Invited lecture 3: Translating gestational thyroid physiology into clinical epidemiological studies**
Dr. Tim Korevaar (Erasmus Medical Center)
- 11.30 **Delegate Session 5: Fat session: “Good fats vs. bad fats”**
- 11.20 **Introduction European Young Endocrine Scientists (EYES) & ESE Summer School**
Eva Coopmans (Board member JNVE)
- 12.30 **Invited lecture 4: Adipose tissue dysfunction in obesity: the role of adipose tissue oxygenation**
Dr. Gijs Goossens (Maastricht University)
- 13.15 **Lunch**
- 14.00 **Gildeprint: How to print your thesis**
- 14.15 **Delegate Session 6: Steroid hormones session: “From steroid hormone to transgender”**
- 15.30 **Evaluation, JNVE award and farewell**

Delegate Session 3:

Bone session: "I found this rather humerus"

Chairs: Eva Coopmans and Thamara Osinga

9. The 24-hour serum profiles of bone markers in healthy older men and women

Evie van der Spoel (LUMC)

10. Pre-analytical stability of FGF23 with today's immunoassays

Niek F. Dirks (LUMC)

11. Circadian rhythms are essential for healthy bone tissue

Maaïke Schilperoort (LUMC)

12. Fracture risk is not increased in transwomen and transmen receiving long-term gender-affirming hormonal treatment: a nationwide cohort study

Chantal M. Wiepjes (Amsterdam UMC)

Delegate Session 4:

Thyroid session: "It's a (para)thyroid thing?"

Chairs: Charlotte Heinen and Anouk van Berkel

13. Critical evaluation of the Dutch Neonatal screening on Central Congenital Hypothyroidism

Kevin Stroek (Amsterdam UMC)

14. Mortality in children with early-detected congenital hypothyroidism of central origin

Jolanda C. Naafs (Amsterdam UMC)

15. Evaluation of the Performance of the 2015 American Thyroid Association Guideline in High Risk Thyroid Cancer Patients

Evert F.S. van Velsen (Erasmus MC)

16. The Effect of Vitamin D Supplementation on Plasma Non-Oxidised PTH in a Randomized Clinical Trial

Stan Ursem (Amsterdam UMC)

Delegate Session 5:

Fat session: “Good fats vs. bad fats”

Chairs: Mariska Vlot and Eva Coopmans

17. Inhibition of the endocannabinoid system activates brown fat and attenuates dyslipidemia

Robin van Eenige (LUMC)

18. MR depletion leads to weight loss and brown fat activation in male mice

Lisa L. Koorneef (LUMC)

19. Unique homozygous SNRPN point mutation as a potential new cause of prader-willi (like) syndrome

Karlijn Pellikaan (Erasmus MC)

20. Body composition in patients with craniopharyngioma: is DXA-scanning necessary for evaluating the metabolic syndrome?

Selveta S. van Santen (Erasmus MC)

21. A comprehensive diagnostic approach to detect underlying causes of obesity in adults

Eline S. van der Valk (Erasmus MC)

Delegate Session 6:

Steroid hormones session: “From steroid hormone to transgender”

Chairs: Mark van Treijen and Dirk van Moorsel

22. The effect of corticosteroids on human choroidal endothelial cells: a model to study central serous chorioretinopathy

Joost Brinks (LUMC)

23. Blood in magnets: method development for untargeted plasma NMR metabolomics of adrenal hypertension

Nikolaos G. Bliziotis (Radboud UMC)

24. Diagnosis of Cushing’s Syndrome: Cut-off values of screening tests revisited

Martijn Dane (LUMC)

25. PRolaCT – a Prolactinoma Randomized Clinical Trial comparing Endoscopic Trans-sphenoidal Surgery with Dopamine Agonists, a study protocol

Ingrid M. Zandbergen (LUMC)

26. Hormone treatment with estrogen and testosterone induces facial feminization in transwomen and masculinization in transmen: quantification by 3D scanning and patient reported outcome measures

Marieke Tebbens (Amsterdam UMC)

27. Mortality in transgender people receiving hormone treatment: results of a nationwide cohort study

Christel J.M. de Blok (Amsterdam UMC)

Contact information:

JNVE-website: <http://www.nve.nl/de-jnve>

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If there are any questions during the conference please contact: Charlotte Heinen (06-52110086)



Venue and hotel accommodation:

Van der Valk Hotel Nijmegen-Lent

Hertog Eduardplein 4
6663 AN Nijmegen

Phone number: +31247920200

Website: <https://www.valknijmegen.nl>

Shortest route to the hotel by car:

Van der Valk Hotel Nijmegen-Lent is accessible via the motorways A15, A50 and A325.

From the South (Eindhoven, Den Bosch) follow the A50 towards junction Valburg. Exit the junction and take the A15 to the East. Exit at junction Ressen and take the A325 towards Nijmegen-Noord/Lent. At the third sets of traffic lights turn left and at the next traffic light turn right. The hotel is located at your right.

From the North (Arnhem, Apeldoorn) you follow the A325 towards Nijmegen- Noord/Lent. At the third sets of traffic lights turn left (Prins Mauritssingel) and at the next traffic light turn right (station Lent). The hotel is located at your right. Please be careful by crossing the bicycle path!

Shortes route to the hotel bij public transport:

Train: Van der Valk Hotel Nijmegen-Lent is located directly at Nijmegen Lent station and perfectly accessible with public transport. The station is situated between Nijmegen and Arnhem Central.

Bus: The bus stop next to the hotel offers a direct connection with Arnhem Central Station as well as Nijmegen Central Station.





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GILDEPRINT

Abstracts

1. Early detection of hypoglycemia in type 1 diabetes using a wearable device measuring heart rate variability

Marleen Olde Bekkink¹, Mats Koeneman², Bastiaan E de Galan¹, Bas S.J. Bredie¹

¹Radboudumc, department of Internal Medicine, Nijmegen, Netherlands.

²Radboudumc, Reshape Center of Innovation, Nijmegen, Netherlands.

Background: Patients with type 1 diabetes (T1D) are at risk of severe, potentially hazardous, hypoglycemia. Changes in heart rate variability (HRV) patterns occur at the initiation of hypoglycemia due to sympathetic nervous system activity.

Objective: We aimed to investigate the potential use of HRV- detection by a wearable device as an early alert for hypoglycemic events.

Methods: Proof of principle study including 23 patients with T1D. Patients were asked to wear the VitalConnect HealthPatch on the chest during five consecutive days. Hypoglycemic events were defined as glucose ≤ 3.9 mmol/l by finger stick measurement and verified by continuous glucose monitoring. Changes in HRV were retrospectively evaluated in standardized periods before a hypoglycemia was recorded.

Results: 66 hypoglycemic events were recorded by 23 patients (14 women, age 42 ± 11 years, diabetes duration 26 ± 10 years). Hypoglycemia caused a clear detectable increase in LF:HF or decrease in RMSSD in 36 (55%) of the hypoglycemic events. Eighteen hypoglycemic events (27%) showed the opposite, i.e. a clear decrease in LF:HF and increase in RMSSD. Ten events (15%) contained insufficient data to determine changes in HRV. There were 2 events (3%) that did not display a change in either LF:HF or RMSSD.

Conclusion: Hypoglycemic are preceded by changes in HRV that can be detected by a wearable device in patients with type 1 diabetes. Wearable devices measuring real time HRV seem promising devices for early detection of hypoglycemic events.

2. Serum metabolites associated with fasting and postprandial measures of glucose metabolism in a non-diabetic population

Maxime M Bos¹, Raymond Noordam¹, Katie Bennet², Marian Beekman³, Eline Slagboom³, Torbjörn Lundstedt², Izabella Surowiec², Diana van Heemst¹

¹Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands.

²AcureOmics AB, Umeå, Sweden.

³Department of Medical Statistics and Bioinformatics, Section of Molecular Epidemiology, Leiden, The Netherlands.

Introduction: Blood metabolic profiling is a promising approach for gaining novel insights into early metabolic changes preceding the onset of diabetes and for the detection of early markers for insulin resistance. Therefore, we aimed to identify blood metabolites associated with different aspects of glucose regulation in non-diabetic individuals.

Methods: This study was conducted in a subset of non-diabetic middle-aged participants from the Leiden Longevity Study (N = 202). We analyzed 192 metabolites from two metabolomics platforms, including metabolites from several different chemical classes, like acylcarnitines, glycerophospholipids, sphingolipids, amino acids and fatty acids. Linear regression analyses were performed to assess associations between different measures of glucose metabolism (fasting glucose, fasting insulin, HOMA-IR, Matsuda Index, Insulinogenic Index and HbA1c) and fasting serum metabolites adjusted for age, sex and BMI.

Results: We identified 22 metabolites associated with different fasting and postprandial measures of glucose metabolism. Ten metabolites, including for example hexadecanoic acid and tyrosine, were associated with higher fasting glucose and five metabolites, including for example glutamine and glycine metabolites, were associated with lower fasting glucose. Alanine, lactic acid, tryptophan, phenylalanine, tyrosine, uric acid, valine and alpha-ketoglutaric acid were positively associated with fasting insulin and the Matsuda Index. Of these eight metabolites, all but valine was associated with higher HOMA-IR. Moreover, we observed alanine and proline to be associated with a higher Insulinogenic Index. In addition, 1,5-anhydro-d-glucitol and threonine were associated with lower HbA1c.

Conclusion: Of the metabolites associated with measures of glucose metabolism, alpha-ketoglutaric acid and threonine have not been related to diabetes previously, therefore, requiring further studies. Once replicated, our results may improve understanding of the mechanisms involved in disease etiology and thereby improving treatment possibilities.

3. C-peptide response to multiple stimuli in long-standing type 1a diabetes

Bas Uitbeijerse¹, Michiel Nijhoff¹, Eelco de Koning¹

¹Department of internal Medicine, LUMC, Leiden, The Netherlands.

Background: There is mounting evidence for residual β -cell mass in a significant portion of patients with long-standing type 1 diabetes (T1D). Residual β -cell function is associated with improved glycemic control including a lower risk of hypoglycemia and microvascular complications. It is unknown whether these β -cells function normally. Here we aim to determine the β -cell response to various physiological and other β -cell secretagogues.

Methods: Male patients with auto-antibody positive T1D and diabetes duration ≥ 5 years were included. On day one, a mixed meal test (MMT) was performed, followed by an arginine bolus. On day two, a three-phase clamp was performed: 1. euglycemia (5 mmol/L), 2. hyperglycemia (14 mmol/L) and 3. hyperglycemia+GLP-1 (1.5 pmol/kg/min) infusion. Arginine boluses were given at the end of every phase. An ultra-sensitive C-peptide assay was used.

Results: Fifteen patients were included (age: 34.9 ± 9.3 years, diabetes duration: 18.7 ± 9.4 years). C-peptide was detected at all time points in 2/15 participants. In 3/15 participants, C-peptide only became detectable after varying stimuli. Age, diabetes duration, age at diagnosis and BMI were not statistically different in the 5 C-peptide positive patients as compared to the C-peptide negative patients. On day 2, C-peptide did not show a first phase response to glucose, but C-peptide did increase eventually 2.9 fold [95% CI 1.2;7.1] during the hyperglycemic phase and 3.5 fold [95% CI 2.4;5.2] during the hyperglycemia+GLP-1 infusion. During all phases arginine further stimulated C-peptide. On day 1, the MMT increased C-peptide 6.7 fold [95% CI 1.1;42.4]. The subsequent arginine bolus further stimulated C-peptide 2.2 fold [95% CI 1.2;4.1]. C-peptide was detectable in the same 5 patients during the two study days.

Conclusion: In patients with T1D and detectable C-peptide, different secretagogues (glucose, GLP1, arginine) can stimulate β -cells, but a first-phase response to glucose was absent. An MMT followed by an arginine bolus is sufficient to uncover residual β -cell function in T1D.

4. Pasireotide LAR treatment in an dopamine-resistant and aggressive prolactinoma with excellent response

Sebastiaan W.F. van Meyel¹, E.C. Coopmans¹, K.J. Pieterman², A.J. van der Lely¹, S.J.C.M.M. Neggers¹

¹Department of Internal Medicine, Endocrinology section, Pituitary Centre Rotterdam, Erasmus University Medical Centre, Rotterdam, the Netherlands

²Departments of Radiology and Medical Informatics, Biomedical Imaging Group Rotterdam, the Netherlands

Background: Prolactinoma is the most common secreting pituitary adenoma, and hyperprolactinemia may result in hypogonadism, infertility and galactorrhea, or it may remain asymptomatic. Cabergoline is considered the mainstay medical treatment and transsphenoidal surgery (TSS) is recommended for patients that are medically resistant to dopamine agonist therapy.

Pasireotide LAR (PAS) is a recently developed 2nd generation multi-somatostatin receptor (SSTR) ligand. Existing literature already indicated a positive effect of PAS in the control of aggressive pituitary adenomas. In vitro, PAS inhibited prolactin secretion significantly more than 1st generation SST analogues. However, most of dopamine-resistant prolactinomas appear to express no or low levels of SSTR5 and are resistant to SST analogues that bind to this receptor. Furthermore, there was no additive effect on prolactin secretion when a SSTR5 inhibitor was added to a dopamine agonist.

Case presentation:

A 61-year-old woman was referred for evaluation of a dopamine agonist-resistant prolactinoma. Initially she presented to a peripheral hospital in 1993 with a history of secondary amenorrhea since the age of 25, there were no other clinical features of hyperprolactinemia. At clinical examination there was no indication that eluded thyroid goiter and systemic examination was normal. Her laboratory results showed hyperprolactinemia and other hormonal axes were within the reference range. The MRI revealed a macro-adenoma in the anterior lobe of the pituitary.

In the peripheral hospital the patient received two times TSS and two times radiosurgery. She was also treated with dopamine agonists (1.0 mg/3xwk), but her prolactin levels kept elevated. At our institution we also tried therapies of dopamine agonists as well as in combination with 1st generation SST analogues. This again appeared to be unsuccessful. As a last resort, before the use of temozolomide, we attempted PAS in combination with cabergoline to which our patient responded excellently.

Immunohistochemistry showing membranous expression score of IRS 9 for SSTR2 and IRS 12 for SSTR5 and a strong reactivity for prolactin.

Conclusion: PAS therapy holds potential in dopamine agonist- and 1st generation SST analogues resistant prolactinomas that express high affinity for SSTR5. Furthermore, switching to PAS can be considered in patients with an aggressive tumor as a next treatment step before starting with Temozolomide.

5. Differential co-regulator recruitment by glucocorticoid receptor modulators and effects on memory consolidation

Eva Viho¹, Rob Buurstede¹, Jan Kroon¹, René Houtman², Onno C. Meijer¹

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Background: After stress exposure, prolonged or excessive exposure to glucocorticoids has been consistently related to increased vulnerability to psychopathologic disorders (Zalachoras, 2013). Therefore, glucocorticoid receptor (GR) antagonism was predicted to have considerable therapeutic value in stress-related psychopathologies (De Kloet, 2005). Unlike full GR agonists or antagonists, selective glucocorticoid receptor modulators (SGRMs) are ligands that combine agonistic and antagonistic properties and are thereby able to separate beneficial from harmful treatment effects (Zalachoras, 2013). GR transcription specificity of the SGRMs is supported by the diversity of recruited coregulatory factors. CORT118335 and CORT108297 are two SGRMs that lead to opposite consequences on memory consolidation.

Objectives and Hypotheses: In this project we compared the GR co-regulators recruitment profiles of CORT118335 and CORT108297. We expect that respectively the antagonistic and agonistic properties are reflected by coregulatory interactions.

Methods: Coregulatory factors recruitment profiles were obtained using the MARCoNI technology.

Results: CORT118335 and CORT108297 differ significantly in their recruitment profile for 17/67 co-regulators. CORT118335 preferentially recruited 4, particularly the CREB Binding Protein (CBP). CORT108297 preferentially recruited 13 co-regulators at the GR, including Nuclear Receptor Coactivators (NCOA) 2, 3 and 6.

Conclusion: Differences in coregulatory recruitment could underlie the differential effects of CORT118335 and CORT108297 on memory consolidation.

6. Glucocorticoid receptor-regulated transcription in metabolic tissues is modulated by androgen receptor signaling

Jan Kroon¹, Mark Nixon², Brian Walker², Onno Meijer¹

¹Department of Medicine, Division of Endocrinology, Leiden University Medical Centre, Leiden, the Netherlands;

²BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom

Background: Glucocorticoids exert a myriad of metabolic effects mediated predominantly via binding to the glucocorticoid receptor (GR). The GR is known to exert sexually dimorphic effects, possibly via interaction with the androgen receptor (AR), but it is unclear if such crosstalk plays a role in metabolic tissues.

Objective and hypotheses: Our objective is to investigate if glucocorticoid-androgen crosstalk exists in metabolic tissues. We hypothesize that androgens modulate GR signaling in metabolic tissues.

Methods: We collected metabolic tissues from male C57BL/6J mice (N=6-7/group) subjected to: 1) vehicle-treatment, 2) GR agonist corticosterone, 3) corticosterone + AR agonist dihydrotestosterone and 4) corticosterone + AR antagonist enzalutamide. Local glucocorticoid levels were determined by mass spectrometry. Expression of glucocorticoid-responsive genes in white adipose tissue (WAT), liver and brown adipose tissue (BAT) was determined by RT-qPCR and western blot. To evaluate crosstalk in vitro, cultured white and brown adipocytes were incubated with a combination of glucocorticoids and androgens and expression of glucocorticoid-responsive genes was determined by RT-qPCR.

Results: AR agonism enhances GR-regulated transcription in vitro in cultured white and brown adipocytes and in vivo in WAT and BAT. Conversely, AR antagonism attenuates GR-regulated transcription in WAT and liver. In WAT, we found that AR antagonism lowers active glucocorticoid levels via inhibition of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1)-mediated turnover. In liver, attenuated GR activity was independent of 11 β -HSD1 status and glucocorticoid ligand levels.

Conclusion: We show that glucocorticoid-androgen crosstalk exists in metabolic tissues. The mechanisms underlying this are tissue-specific. Further research is warranted to delineate the relative contribution of glucocorticoid-androgen crosstalk to metabolic pathways.

7. A short-list of GR and CREB targets implicated in glucocorticoid-enhanced memory consolidation in the male rat brain.

Rob J.C. Buurstedde¹, Lisa T.C.M. van Weert¹, Eva Viho¹, Szymon M Kielbasa², Ioannis Moustakas³, Hailiang Mei³, Benno Roozendaal⁴, Onno C Meijer¹

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⁴Department of Cognitive Neuroscience, RUMC, Nijmegen, The Netherlands.

Background: Glucocorticoids potently enhance memory consolidation after emotional events, in a strictly noradrenaline-dependent way. This suggests an interaction of two transcription factors on the genome: the glucocorticoid receptor (GR) and cAMP response binding protein (CREB). Even though the involvement of both factors has been established, their possible interactions at the genome and their transcriptional targets important for consolidation of emotional memories remain undiscovered.

Objective: Our current project focuses on identifying the binding sites of these transcription factors in the rat hippocampus, in an in vivo setting where additional GR activation acts as a switch for memory consolidation.

Methods: Male Sprague Dawley rats (n=4/group) received either object location memory (OLM) training or no training, combined with a vehicle or a 3.0mg/kg corticosterone injection (I.P.) 45 minutes prior to sacrifice. This factorial design enables to study the separate effects of OLM training (CREB activation) and corticosterone injection (GR activation) as well as their interactions. GR and CREB targeted Chromatin ImmunoPrecipitation Sequencing (ChIP-Seq) was performed on the hippocampi of these rats to identify their genomic binding sites. The genomic binding sites that were present in at least 3 out of 4 biological replicates were used in the downstream analysis and annotated to the nearest gene.

Results: Analysis of the ChIP-Seq data reveals limited context dependence of DNA binding of both transcription factors. Due to the high basal levels of corticosterone, only a limited (<50) number of loci showed an increase in GR binding, resulting in a short-list of GR putative target genes. 8 out of 10 tested GR-binding associated genes were found to be activated by corticosterone in a separate mouse study.

Conclusion: These direct GR target genes may play a role in the process of glucocorticoid-enhanced memory consolidation and provides new leads to further unravel the mechanism underlying this process.

8. The effects of dexamethasone on glucocorticoid and mineralocorticoid receptors in human pediatric hippocampus

Anne-Sophie C.A.M. Koning¹, Marit Bogaards¹, Lisa L. Koorneef¹, Philippe C. Habets¹, Hetty C.M. Sips¹, Lianne van der Wee-Pals¹, Judith M. de Bont², Hanneke M. van Santen³, Onno C. Meijer¹

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³UMCU, Department of Pediatric Endocrinology, Utrecht, Netherlands.

Background: Dexamethasone (DEX) is a commonly used drug, but can cause severe neuropsychiatric effects, like depression, delirium and mania. As DEX is a glucocorticoid receptor (GR) agonist, it suppresses the production of cortisol and thereby depletes the mineralocorticoid receptor (MR) of its ligand, rendering MR inactive. Next to the strongly stimulated GR, the reduced MR activity by DEX might be the cause of the neuropsychiatric effects.

Objective and hypotheses: The aim of this study was to investigate the expression and functionality of GR and MR in the brain of a DEX-treated patient and unaffected controls. It was hypothesized that MR target gene expression in the DEX-treated patient is reduced, because of the absence of cortisol, whereas GR target gene expression was expected to be high.

Methods: Frozen and paraffin embedded hippocampal tissue from an 8-year-old brain tumor patient treated with DEX was obtained from the VUmc biobank. Paraffin embedded hippocampal tissue from 2 unaffected controls was obtained from the Department of Pathology of the LUMC. Frozen hippocampal tissue from 8 unaffected controls was obtained from the NIH NeuroBioBank at the University of Maryland, Baltimore, MD. Expression and functionality of GR and MR was analyzed with q-PCR, immunohistochemistry and immunofluorescence.

Results: In DEX-treated tissue q-PCR analyses showed low expression of MR target genes, whereas expression of classical GR target genes was high. Despite the low MR target gene expression, immunohistochemistry and immunofluorescence analyses showed nuclear staining for both GR and MR, suggesting activation of both receptors to an extent that allow nuclear translocation.

Conclusion: In human pediatric hippocampal tissue treated with DEX, low MR target gene expression is seen. DEX does seem to be able to cause nuclear translocation of MR, but does not induce expression of MR target genes. Currently, an RCT is set up to investigate the MR refill concept: adding hydrocortisone to DEX to restore MR activity and thereby reducing the adverse neuropsychological effects.

9. The 24-hour serum profiles of bone markers in healthy older men and women

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Background: The process of bone turnover displays variations over 24 hours, with C-terminal cross-linked telopeptide of type 1 collagen (CTX) and osteocalcin exhibiting a nadir in the afternoon and a peak in the night. In contrast, N-terminal propeptide of type 1 procollagen (P1NP) did not display an apparent 24-hour rhythm. Other emerging novel biomarkers of bone, sclerostin and Dickkopf-related protein 1 (DKK1), are markers of osteocyte activity with limited data available regarding their 24-hour profiles.

Objective and hypotheses: In this study, we aimed to extend available data on 24-hour profiles of CTX, osteocalcin, and P1NP and to assess the 24-hour profiles of sclerostin and DKK1 in healthy older men and women and to compare these between men and women.

Methods: We measured five bone markers, CTX, osteocalcin, P1NP, sclerostin, and DKK1, in EDTA plasma collected every 4 hours during 24 hours in 37 healthy older men and women (range 52–76 years). Differences between time points were determined using repeated measures ANOVA and cosinor analyses were performed to determine circadian rhythmicity.

Results: The circadian rhythm of CTX was confirmed by the cosinor model, with women showing larger amplitude compared to men. Osteocalcin showed higher levels during night-time compared to daytime in both men and women. For P1NP levels we observed a small but significant increase in the night in men. Sclerostin and DKK1 did not show a circadian rhythm, but sclerostin levels differed between time points. Because of the large intraindividual variation, DKK1 as measured in this study cannot be considered a reliable marker for diagnostic or research purposes.

Conclusion: In conclusion, when measuring CTX, osteocalcin, P1NP, or sclerostin either in clinical practice or in a research setting, one should consider the 24-hour profiles of these bone markers.

10. Pre-analytical stability of FGF23 with today's immunoassays.

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Background: The bone-derived hormone fibroblast growth factor 23 (FGF23) controls phosphorus and vitamin D homeostasis and is used as a marker in chronic kidney disease/dialysis research. It is rarely requested diagnostically, but important in case of unexplained hyperphosphatemia. For determination of FGF23, we currently rely on four immunoassay manufacturers. Immutopics, Kainos, Millipore and DiaSorin have all marketed assays for determination of the intact 251 amino-acid long protein. Additionally, Immutopics has developed an assay which determines both the intact protein and the 72 amino-acid C-terminal fragment of FGF23, formed after cleavage by furin. Unfortunately, these five assays are neither standardized nor harmonized and differ substantially in their reported values. This, in turn, has led to scepticism regarding their suitability in research and particularly clinical diagnostics. One factor that attributes to their lack of comparability and forthcoming questionable legitimacy is the supposed instability of intact FGF23 post-venipuncture. This protein instability may emerge in whole blood, before centrifugation and removal of blood cells and clotting factors, and/or after centrifugation, in serum or plasma.

Objective and hypotheses: Various studies have reported their finding regarding this matter, but results have not always agreed. We have therefore performed additional experiments to elucidate some of the inconsistencies and account for the still remaining hiatus we observed in the available literature.

Results: We concluded FGF23 instability does not seem to be an issue any longer after introduction of the 2nd generation intact and C-terminal FGF23 assays by Immutopics and the automated intact FGF23 assay from Diasorin. Addition of protease inhibitors in the collection tubes to prevent degradation is not required. Centrifugation and subsequent removal of blood cells and clotting factor should nonetheless not be delayed, but completed within 30 min to one hour to prevent regression of the antibodies' effectiveness to recognize FGF23. After centrifugation, protein instability does no longer progresses.

11. Circadian rhythms are essential for healthy bone tissue

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Aim: The past decade, it has become evident that circadian (i.e. 24 h) rhythms within metabolically active tissues are very important for physical health. However, although shift work has been associated with osteoporosis, circadian rhythmicity has not yet been extensively studied in the field of bone research.

Methods & Results: In this study, we investigated which genes are rhythmically expressed in bone, and whether circadian disruption by means of alternating light-dark cycles affects bone turnover and structure in mice. Our results demonstrate diurnal expression patterns of clock genes (*Rev-erb α* , *Bmal1*, *Per1*, *Per2*, *Cry1*, *Clock*), as well as genes involved in osteoclastogenesis, osteoclast proliferation and function (*Rankl*, *Opg*, *Ctsk*) and osteocyte function (*c-Fos*) in bone. Alternating light-dark cycles caused a reduction in plasma levels of procollagen type 1 amino-terminal propeptide (P1NP) and tartrate-resistant acidic phosphatase (TRAP), suggestive of a reduced bone formation and bone resorption, respectively. These effects coincided with an altered trabecular bone structure and a decreased bending strength as determined by micro-CT after 16 weeks of alternating light-dark cycles. To investigate whether disruption of glucocorticoid rhythm could be an underlying mechanism by which alternating light-dark cycles affect bone health, we flattened corticosterone rhythm in mice by implanting subcutaneous corticosterone pellets. Indeed, flattening of corticosterone rhythm reduced expression of clock genes (*Rev-erb α* and *Per1*), decreased P1NP plasma levels, and affected trabecular and cortical bone structure.

Conclusion: Collectively, these results suggest that circadian rhythm is important for bone health, and that circadian disruption negatively affects bone turnover markers and bone structure. As a large part of the working population participates in shift work (e.g. almost 30% of workers in the U.S.), this justifies further research on the risk of skeletal disorders associated with circadian disturbances, as well as underlying mechanisms.

12. Fracture risk is not increased in transwomen and transmen receiving long-term gender-affirming hormonal treatment: a nationwide cohort study

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Purpose: Gender-affirming hormonal treatment (HT) in transgender people can influence bone mineral density (BMD). Earlier studies found an increase in BMD in transwomen (male-to-female transgender people), and a maintenance or increase in BMD in transmen (female-to-male transgender people). However, the effects of HT on fracture risk are not known. Therefore we aimed to investigate the fracture incidence in transwomen and transmen using long-term HT and to compare this with an age-matched male and female control population.

Methods: All adult transgender people who started with HT before 2013 in our center were included. This population was linked to a random sample of 5 age-matched control males and 5 age-matched control females. Fracture occurrence in 2013 and 2014 was provided by Statistics Netherlands (CBS), which stores all diagnoses from visits to the hospital emergency rooms nationwide. The occurrence of fractures is expressed as percentages, and relative risks (RR) with 95% confidence intervals (CI) were calculated.

Results: A total of 1,725 transwomen (mean age 50 years, standard deviation (SD) 13 years) who used HT for median 15 years (inter quartile range (IQR) 8 – 23 years) were included. Fractures occurred in 2.5% of the transwomen (n=43), while 1.9% of the age-matched control men (RR 1.33, 95%CI 0.94 – 1.86) and 2.2% of age-matched control women (RR 1.14, 95%CI 0.82 – 1.60) had a fracture. A total of 729 transmen (mean age 44 years, SD 12 years) who used HT for median 14 years (IQR 6 – 23 years) were included. Fractures occurred in 1.4% of the transmen (n=10), while 1.6% of the age-matched control men (RR 0.85, 95%CI 0.43 – 1.66) and 2.0% of age-matched control women (RR 0.69, 95%CI 0.35 – 1.34) had a fracture.

Conclusion: This large population of both transwomen and transmen using long-term HT does not demonstrate an increased fracture risk compared with an age-matched control population. This increases the evidence that HT does not negatively affect bone health.

13. Critical evaluation of the Dutch Neonatal screening on Central Congenital Hypothyroidism

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Background: Congenital hypothyroidism (CH) comprises disorders of either the thyroid gland (CH-T) or the regulatory system stimulating the thyroid gland consisting of the hypothalamus and the pituitary gland (central CH, CH-C). CH results in a shortage of thyroid hormone, which is essential for brain development. For this reason, a neonatal screening program for CH was established in the Netherlands in 1981. The Dutch screening on CH is primarily based on thyroxine (T4) determination in filter paper blood spots. In the lowest 20% of T4 values, TSH levels are measured. Thyroxine binding globulin (TBG) is measured in the lowest 5% of T4 values. A calculated T4/TBG ratio serves as an indirect measure for free T4. Two consecutive abnormal T4/TBG ratios (≤ 17) are indicative of CH-C whereas increased TSH indicates CH-T. Having T4 as a primary marker enables us to identify a large portion of neonates with potential CH-C. However, increasing reports of false positive cases of CH-C require a critical evaluation and exploration of possible improvements of the current program.

Methods: We estimated the contribution of the T4/TBG ratio to the poor specificity of CH screening in 1234 cases referred for CH in the period 2012-2015.

Results: Of 708 referrals, CH-C was established in 17 neonates (true positive rate 2.4%) with a high number of false positives (691). Lowering the T4/TBG ratio cut-off value in the second heel prick to 16, 15, 14, 13 and 12 respectively results in a reduction of 176, 358, 483, 578 and 646 false positives, at the cost of an increase in false negatives of 2, 3, 4, 4 and 5.

Conclusion: Screening on CH-C is mainly based on determination of the T4/TBG ratio. With this study we show that this ratio is a major contributor to the high number of false positive CH-C referrals and thus to the poor specificity of CH screening. Lowering the ratio COV reduces the amount of referrals tremendously, while the increase of missed cases is limited. Thus, adaptation of the COV of the T4/TBG ratio is the first step in improving the specificity of neonatal screening on CH.

14. Mortality in children with early-detected congenital hypothyroidism of central origin

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Background The Dutch neonatal screening program effectively detects both primary and secondary congenital hypothyroidism (CH). This unique feature provides the ability to detect and treat central CH (CH-C) patients early. Approximately 60% to 80% of CH-C patients have multiple pituitary hormone deficiencies (MPHDs), making CH-C a potentially life-threatening disease. However, data on childhood mortality in patients with CH-C are lacking.

Objectives To study the mortality rate in pediatric patients with early-detected and treated CH-C in the Netherlands and to investigate whether causes of death were related to pituitary hormone deficiencies.

Methods Overall mortality rate, infant mortality rate (IMR), and under-5 mortality rate were calculated in all children with CH-C detected by neonatal screening between 1 January 1995 and 1 January 2013. Medical charts were reviewed to establish causes of death.

Results A total of 139 children with CH-C were identified, of which 138 could be traced (82 with MPHD, 56 with isolated CH-C). Total observation time was 1414 years with a median follow-up duration of 10.2 years. The overall mortality rate was 10.9% (15/138). IMR and under-5 mortality rate were 65.2/1000 (9/138) and 101.4/1000 (14/138), respectively, compared with an IMR of 4.7/1000 and under-5 mortality of 5.4/1000 live-born children in the Netherlands during the same time period ($P < 0.0001$). Main causes of death were severe congenital malformations in six patients, asphyxia in two patients, and congenital or early neonatal infection in two patients. Pituitary hormone deficiency was noted as cause of death in only one infant.

Conclusion We report an increased mortality rate in patients with early-detected CH-C that does not seem to be related to endocrine disease. This suggests that mortality due to pituitary insufficiency is low in patients with early-detected and early-treated CH-C.

15. Evaluation of the Performance of the 2015 American Thyroid Association Guideline in High Risk Thyroid Cancer Patients

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Background: The 2015 American Thyroid Association (ATA) risk stratification system for differentiated thyroid cancer (DTC) is designed to predict recurring/persistent disease. Studies evaluating this system comprised relatively few patients with ATA High-Risk and/or follicular thyroid carcinoma.

Objective: Therefore, we aimed to evaluate response to therapy and risk of recurrence in a large population of High-Risk patients.

Methods: Adult patients diagnosed and/or treated for DTC at the Erasmus MC between January 2002 and December 2015, and fulfilling the 2015 ATA High-Risk criteria, were included. Demographical, disease, treatment, ATA response to therapy, recurrence, and mortality characteristics were retrospectively obtained from patient records. Response to therapy after first treatment, recurrence, mortality and radioactive iodine (RAI) refractory percentages were determined. Further, disease specific survival (DSS) was analyzed using the Kaplan-Meier (KM) method.

Results: We included 235 patients (62% women) with ATA High-Risk; 156 patients (66%) had PTC, the others FTC. Mean age was 57 years and median follow-up 71 months. During follow-up, 49 patients (21%) died due to thyroid cancer. After initial therapy, 40 patients (17%) had excellent response, while 121 (52%) had structural disease. And at final follow-up, 72 patients (31%) had excellent response, while 117 (50%) had persistent structural disease. Survival was higher in the initial excellent response than in the initial structural disease group (10-year DSS 100% vs. 58% respectively). Further, 89 patients (38%) developed RAI refractory disease during follow-up, of which 64 (72%) were from the initial structural disease group.

Conclusion: In a population of ATA High-Risk patients, the ATA risk stratification system is an excellent initial predictor for both recurring/persistent disease and mortality. At final follow-up, 50% of the patients had persistent structural disease, while 30% showed excellent response. Furthermore, over 35% of the ATA High-Risk patients developed RAI refractory disease of which the majority had structural disease after initial therapy.

16. The Effect of Vitamin D Supplementation on Plasma Non-Oxidised PTH in a Randomized Clinical Trial

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Objective: PTH can be oxidised in vivo, rendering it biologically inactive. Non-oxidised PTH (n-oxPTH) may therefore give a better image of the hormonal status of the patient. While vitamin D supplementation decreases total PTH (tPTH) concentration, the effect on n-oxPTH concentration is unexplored. We investigated the effect of vitamin D on n-oxPTH concentration in comparison to tPTH and compared the correlations between parameters of calcium, bone and lipid metabolism with n-oxPTH and tPTH.

Design: Randomized clinical trial

Methods: N-oxPTH was measured in 108 vitamin D insufficient (25(OH)D<75 nmol/L) hypertensive patients, treated with vitamin D (2800 IE daily) or placebo for 8 weeks in the Styrian Vitamin D Hypertension Trial (NCT02136771). We calculated the treatment effect and performed correlation analyses of n-oxPTH and tPTH at baseline with parameters of calcium, bone and lipid metabolism.

Results: After treatment, 25(OH)D concentrations increased, tPTH decreased by 9% ($p<0.001$) and n-oxPTH by 7% ($p=0.025$). Also, the ratio of n-oxPTH/tPTH increased ($p=0.027$). N-oxPTH showed a significant correlation with tPTH ($r=0.555$, $p<0.001$), osteocalcin ($r=0.237$, $p=0.014$), HDL ($r=0.254$; $p<0.001$) and triglycerides ($r=-0.216$; $p=0.025$). tPTH had no significant correlation with osteocalcin, HDL or triglycerides.

Conclusions: We showed that both tPTH and n-oxPTH decrease upon vitamin D supplementation. In addition, our study suggests that vitamin D supplementation reduces the oxidation of PTH, as we observed a small but significant decrease in the oxidised proportion of PTH upon treatment. Further research should be carried out to establish the clinical relevance of n-oxPTH and the role of oxidation in PTH-based therapies.

17. Inhibition of the endocannabinoid system activates brown fat and attenuates dyslipidemia

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Aim: The endocannabinoid system (ECS) is involved in various metabolic functions, such as nutrient transport and energy storage. The cannabinoid type 1 receptor (CB1R) inverse agonist rimonabant was identified and sold as an anti-obesity drug, but withdrawn from the market due to psychiatric side effects. Mechanistically, we have shown that rimonabant potentiates the sympathetic activation of brown fat. The aim of the current project is to provide proof that rimonabant attenuates dyslipidemia and atherosclerosis in APOE*3-Leiden.CETP transgenic mice, a well-established mouse model for human-like lipoprotein metabolism.

Methods: Female mice were fed a Western-type diet (containing 16% fat and 0.1% cholesterol) with or without supplementation of 0.017% w/w rimonabant. Body weight and food intake were monitored throughout the study. After 4 weeks, body composition was determined by echo-MRI, and plasma triglycerides (TG) and cholesterol were measured in 4h fasted plasma samples. In addition, we measured energy expenditure by means of indirect calorimetry.

Results: Rimonabant transiently reduced food intake, which normalized after 4 days of treatment, and reduced fat mass after 4 weeks of treatment (-48%, $p < 0.05$). In addition, rimonabant reduced the respiratory quotient during the light period (0.80 vs. 0.82, $p < 0.01$) indicative of increased fatty acid oxidation. As a consequence, rimonabant lowered plasma cholesterol (-31%, $p < 0.05$) and TG (-49%, $p < 0.01$).

Conclusion: In conclusion, rimonabant treatment of cholesterol-fed APOE*3-Leiden.CETP mice alleviates dyslipidemia, probably as a consequence of brown fat activation. Current experiments focus on investigating underlying mechanisms and studying the potential benefit of ECS modulation for atherosclerosis development. We hypothesize that modulating endocannabinoid synthesis and degradation enzymes provides a safe alternative for rimonabant, that can be used in the treatment of both metabolic and cardiovascular disorders.

18. MR depletion leads to weight loss and brown fat activation in male mice

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Background: Glucocorticoids regulate pivotal processes such as metabolism and inflammation via the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). Here we investigated the relative contribution of MR in the regulation of metabolism. To this end, we used synthetic glucocorticoid dexamethasone, which strongly binds to GR but not MR. This completely suppresses endogenous glucocorticoid production thereby depleting MR signalling. To reactivate MR, a low dose of corticosterone was administered as add-on therapy to DEX treatment.

Materials and methods: Male C57BL/6J mice received a high-fat diet (HFD) in combination with 10% fructose water for 24 days. Dexamethasone (DEX, 1 mg/kg/day) was administered via diet-supplementation and corticosterone via subcutaneous implantation of slow-release pellets. Body weight and composition were measured weekly. To investigate peripheral triglyceride uptake, mice were intravenously injected with glycerol tri[³H]oleate-labelled lipoprotein-like emulsion particles and tissues were collected for measurement of ³H-activity, histological analysis and RT-qPCR analysis.

Results: DEX fully prevented HFD-induced body weight gain, which was partially rescued by CORT add-on therapy. DEX with or without CORT add-on therapy similarly increased the uptake of lipoprotein-derived triglycerides in brown adipose tissue (BAT). Interestingly, DEX increased BAT tissue weight and intracellular lipid droplet size stronger than DEX with CORT add-on therapy. In line with this, DEX upregulated expression of BAT marker genes (*Prdm16*, *Pgc1α*, *Ap2*), lipid transporters (*Cd36*, *Lpl*) and rate-limiting lipolysis enzyme *Atgl*, while this was (partially) lost upon CORT add-on therapy.

Conclusion: Our data suggest that MR depletion in the context of high GR via DEX treatment leads to weight loss, partially caused by increased BAT activity. MR reactivation via CORT add-on therapy partially counteracts this. Where MRs act to counteract GR-mediated metabolic effects is for now unknown.

19. Unique homozygous SNRPN point mutation as a potential new cause of prader-willi (like) syndrome

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Introduction: Prader-Willi syndrome (PWS) is a rare condition characterized by hypothalamic dysfunction (leading to hyperphagia, abnormal temperature regulation, abnormal pain registration and pituitary hormone deficiencies) and cognitive impairment. PWS is generally believed to be caused by loss of expression of an entire cluster of paternally expressed genes within the PWS region on chromosome 15, due to deletion, uniparental disomy or imprinting center defects. We describe a unique patient with the complete spectrum of PWS features, in whom these regular causes were ruled out. Additional genetic testing revealed a homozygous point mutation in *SNRPN* (one of the genes located in the PWS region) which was located in a large homozygous region. This patient is unique, because point mutations in a single gene have never been described before as the cause of PWS.

Patients, materials and methods: In the index patient, we performed automated sequencing (as part of obesitome diagnostics), methylation testing, Multiplex Ligation-dependent Probe Amplification (MLPA) analysis and SNP array.

Results: In the 46-year-old index patient, genetic diagnose of PWS was initially rejected after regular genetic tests for PWS showed normal results. Since the patient had nearly all phenotypic features corresponding to PWS, we performed additional genetic testing which revealed a homozygous mutation in *SNRPN*, located in a large homozygous region on chromosome 15. The parents of the patient turned out to be first-degree relatives.

Conclusion: Until now, it was generally accepted that Prader-Willi syndrome could only be caused by functional loss of an entire cluster of genes within the PWS region on chromosome 15q11.2-q13. The unique finding of a homozygous point mutation in a single gene of this region (*SNRPN*) in a patient with virtually all features of PWS, means a revolutionary change in our knowledge of the pathophysiology of the syndrome.

20. Body composition in patients with craniopharyngioma: is DXA-scanning necessary for evaluating the metabolic syndrome?

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Craniopharyngiomas (CP) are benign tumors in the sellar region with an aggressive local behavior. CP patients with have an adverse metabolic profile due to hypothalamic damage and pituitary deficiencies. Obesity is an important feature of the metabolic syndrome (MetS). In earlier research, the prevalence of MetS was 46% in CP patients, which is significantly higher than for the general population (15% in the Swedish and 26% in Dutch population). However, in this research, increased BMI was used as a as definition for obesity. BMI does not take body composition into account. BMI misclassifies more than 50% of childhood cancer survivors as normal, while DXA observes an increased body fat percentage (BF%) (Blijdorp 2012). Our hypothesis is that MetS (as before defined by IDFTFEP and others (Alberti 2009; Wijnen 2017) and adiposity is underestimated in our cohort of 95 CP patients by simply using BMI. In the present retrospective cross-sectional study, the MetS criterion obesity was defined based on BMI (A) and DXA-measured BF% (B) and fat mass index (FMI) (C) at first DXA-scan (FD) and last DXA-scan (LD). MetS was higher compared to the general population in all definitions (at LD respectively A 47% vs. 22%; $P < 0.05$, B 46% vs. 20%, $P < 0.05$, C 54% vs. 19%, $P < 0.05$). A Cohen's kappa measurement of agreement was set out with MetS and obesity. For MetS, an almost perfect agreement was found if increased BMI was compared with either increased BF% (Kappa 0.82-0.88, $P < 0.001$) or FMI (Kappa 0.85-0.88, $P < 0.001$). For obesity, agreement is fair (Kappa 0.37, $P = 0.002$ at LD) to moderate (Kappa 0.53, $P < 0.001$ at FD) if BMI is compared BF%. Occurrence of MetS was significantly lower when measured with FMI compared to BMI at FD (40% vs. 43%, $P < 0.001$), but higher at LD (45% vs. 40%, $P < 0.001$) and higher when BF% is compared to BMI (51% vs. 45%, $P < 0.001$ at FD, 47% vs. 40%, $P < 0.001$ at LD). In conclusion, CP patients are at risk for the MetS. Although occurrence of the MetS is even higher if estimated with BF% by DXA-scan, agreement when defined with BMI is good.

21. A comprehensive diagnostic approach to detect underlying causes of obesity in adults

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Obesity is a worldwide growing problem. When confronted with obesity, many physicians focus on treatment of the (consequences of) adiposity. We plead for an individualized treatment after adequate diagnostics.

We provide experience-based and evidence-based practical recommendations illustrated by clinical examples, about adequate diagnostics in patients with obesity, to detect potential underlying diseases and/or contributing factors. Adult patients consulting a doctor for weight gain or obesity should be assessed for underlying diseases, such as monogenetic or syndromic obesity, hypothyroidism, (cyclic) Cushing syndrome, PCOS, hypogonadism, growth hormone deficiency, and hypothalamic obesity. The most important alarm symptoms for genetic obesity are early onset obesity, dysmorphic features/congenital malformations with or without intellectual deficit, behavioral problems, hyperphagia and/or striking family history.

Furthermore contributing causes should be investigated, including medication (mainly psychiatric drugs, (local) corticosteroids, insulin, and specific β -adrenergic receptor blockers), sleeping habits and quality, shift work, crash diets and yoyo-effect, pregnancy or menopause, smoking cessation and alcoholism. Other conditions associated with obesity include mental factors such as chronic stress or binge-eating disorder and depression.

Identifying and optimizing the underlying diseases, contributing factors, and other associated conditions may not only result in more effective and personalized treatment, but could also reduce the social stigma for patients with obesity.

23. The effect of corticosteroids on human choroidal endothelial cells: a model to study central serous chorioretinopathy

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Purpose: Central serous chorioretinopathy is a chorioretinal disease, of which the exact pathogenesis is unknown. The disease originates in the choroid, with secondary dysfunction of the retinal pigment epithelium, resulting in accumulation of subretinal fluid. Exposure to corticosteroids forms the most important risk factor for central serous chorioretinopathy. We developed a cell model to study the role of corticosteroids in central serous chorioretinopathy.

Methods: Choroidal endothelial cells were isolated from cadaveric human donors. Magnetic-activated cell sorting with anti-human CD31 was performed for choroidal endothelial cell isolation. Isolated choroidal endothelial cells formed capillary-like structures in Matrigel and expressed endothelial cell-specific markers. Primary cultures of purified choroidal endothelial cells treated with intermittent administration of 10⁻⁷ M cortisol were analysed for the effect on both direct and downstream putative corticosteroid responsive genes (FKBP5, PER1, GILZ1, and SGK1).

Results: We found that intermittent administration of 10⁻⁷ M cortisol (mimicking the in vivo situation with diurnal rhythm in blood cortisol levels) led to significant transcriptional upregulation of validated cortisol target genes. Further pharmacological analysis identified the glucocorticoid receptor rather than the mineralocorticoid receptor as the mediator of the cortisol effect on gene expression.

Conclusion: In this study we describe an optimized choroidal endothelial cell isolation and culturing protocol. This *ex vivo* model appears to be very suitable for studying both central serous chorioretinopathy, and other diseases in which corticosteroids and choroidal endothelial cells are involved.

24. Blood in magnets: method development for untargeted plasma NMR metabolomics of adrenal hypertension

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Background and Aim: Several forms of adrenal hypertension, including Pheochromocytoma (PPGL) and Primary Aldosteronism (PA) have been described, and they all share an abnormally high blood pressure as a symptom coupled with an endocrine underlying cause. Even though these diseases are associated with cardiovascular and metabolic complications, current diagnostic approaches often fail to detect them in time. Nuclear Magnetic Resonance Spectroscopy (NMR) has proven to be a valuable tool in the discovery and quantification of disease-related biomarkers, but a reform of the traditionally used protocol was necessary for applying NMR metabolomics on a large set of plasma samples collected for studying adrenal hypertension. To this end, we compared the results from several methods aimed at focusing on small polar metabolites and preparing spectra for multivariate data analysis. The resulting protocol consists of a novel combination of a NMR experiment, a seldom used internal standard for metabolite quantitation, and a data processing routine.

Materials and Methods: Plasma was collected from four patients, two of which suffered from PA and the other two from PPGL. Pooling the plasma from each set of two patients and subsequently aliquoting it, resulted in the creation of two groups, each consisting of 10 replicate samples. These were either subjected to the traditional ultrafiltration approach to remove proteins and lipids altogether, or left unfiltered for analysis with NMR experiments CPMG and LED for removing only the signals originating from the macromolecules. A new internal standard, Maleic Acid, was added to the buffer solution for absolute quantification of metabolites, and its peak compared to that of the commonly used internal standard, TSP, which is known to broaden in the presence of macromolecules, thus hindering quantification. Spectra were recorded on a Bruker Avance III, operating at 500 MHz, and next underwent data reduction using the SPEAQ R package for peak picking and alignment. Results were assessed using the broker Topspin software for spectral inspection and the SIMCA-P software for Principal Component Analysis (PCA).

Results: Both CPMG and LED spectra were deprived from high signals arising from proteins and lipids, indicating the capability of both methods to suppress macromolecule peaks. Maleic acid did not display any peak broadening, in contrast to the traditional quantification standard. PCA models show the metabolic signature of the LED method being closer than CPMG to the ultrafiltration. The LED approach was also able to successfully differentiate the groups of samples, with an adequately low within group variance and a high between group variance.

Conclusions: Overall, our results indicate that by adding Maleic Acid as an internal standard to unfiltered plasma samples, using LED NMR spectroscopy and the SPEAQ data processing pipeline, we were able to achieve a clear separation of PPGL from PA samples according to statistical models with a high degree of variation explained and a high predictive ability. The LED experiment was capable of suppressing protein and lipid signals, indicating its applicability in plasma metabolomics. The fact that Maleic Acid gave rise to a peak that was unaffected by the presence of macromolecules, shows that it is a reliable standard for quantification. With its speed, affordability and ease of use, this complete approach is well suited for large scale metabolomics studies in group differentiation, sample stratification, and putative metabolite quantification. This research is expected to prove valuable in providing the means for upgrading the diagnosis of the different forms of adrenal hypertension.

25. Diagnosis of Cushing's Syndrome: Cut-off values of screening tests revisited

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Background: In order to diagnose Cushing's Syndrome in patients with multiple and progressive features compatible with the syndrome or an adrenal incidentaloma, three screening tests are routinely used: urinary cortisol (2x 24 hrs), late night salivary cortisol (2x) and the 1 mg overnight dexamethasone suppression test. The evidence for the cut-off values used for these tests was mainly obtained years ago with now obsolete methods.

Objective and hypotheses: The objective of this study was to re-examine the validity of these values using state of the art methods traceable to international reference methods and/or international reference standards.

Methods: For this purpose a retrospective cohort study was conducted. Since January 2016 all patients suspected for Cushing's syndrome were screened using urinary cortisol (LC-MSMS), dexamethasone suppression test and salivary cortisol (CORT II, Roche Diagnostics). Final diagnosis was based on laboratory data, clinical data, radiological data and pathological findings after operation. Using the results extracted from the laboratory information system and the final diagnosis, a ROC-curve was generated and the optimal cut-off values were calculated for each screening test.

Results: A total of 243 patients were screened for Cushing Syndrome. Of these, 22 were diagnosed with Cushing's Syndrome (laboratory results based on current reference limits and clinical data confirming diagnosis). Since these tests are used for Cushing screening we aim at a 100% sensitivity. The newly calculated cut-off values were: 123 nmol/L for the dexamethasone suppression test (spec. 97.2%), 5.7 nmol/L for the salivary cortisol (spec. 93%) and 101 nmol/L for the urinary cortisol (spec. 73.4%).

Conclusion: Re-evaluation of the cut-of values for Cushing Syndrome screening resulted in a higher cut-off value for the dexamethasone suppression test (was 50 nmol/L) and a lower cut-off value for urinary cortisol (was 150 nmol/L). Discussions regarding specificity at cut-off levels of 50 nmol/L versus 30 nmol/L in the dexamethason suppression test thus seem futile.

26. PRolaCT – a Prolactinoma Randomized Clinical Trial comparing Endoscopic Trans-sphenoidal Surgery with Dopamine Agonists, a study protocol

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Background: First line treatment for prolactinoma patients is with a dopamine agonist (DA). Endoscopic trans-sphenoidal resection is reserved for patients with severe side effects or a DA resistant prolactinoma. Most patients need prolonged DA treatment, which often causes side effects. Surgery has a good safety profile and high chance of remission and may thus deserve a more prominent place in the treatment of prolactinomas.

Earlier this year, we have started a multicenter observational cohort study, aimed to inventory several patient-specific outcomes, including health-related quality of life (HRQoL) and disease remission. However, there are no randomized clinical trials (RCTs) that have compared the treatment strategies for prolactinomas. The hypothesis for the current study is that early or upfront surgical resection is superior to DA treatment for HRQoL and remission rate in patients with a non-invasive prolactinoma of limited size.

Study Design: This multicenter RCT will compare endoscopic trans-sphenoidal surgery to standard care in 3 groups of prolactinoma patients at different phases in the disease course: (1) newly diagnosed, treatment naïve patients; (2) patients who have had DA treatment for 4-6 months; and (3) patients who have a persisting prolactinoma after DA treatment for >2 years.

The intervention group will be referred to a neurosurgical expertise center to receive personalized surgical consultation with a multidisciplinary team, designed to guide patients in their treatment choice (continue with surgery or return to DA treatment). The control group will receive standard care (DA treatment) and follow up with their own physician.

At least 200 patients are needed per subgroup to assess our main endpoints, HRQoL at 12 months (during DA treatment vs post-surgery) and remission after 3 years (1-year DA withdrawal vs post-surgery).

For both our cohort study and RCT, we are building a collaborative network containing endocrinologists, gynaecologists and neurosurgeons throughout the Netherlands and abroad. For more information, see www.prolactinoom.nl.

27. Hormone treatment with estrogen and testosterone induces facial feminization in transwomen and masculinization in transmen: quantification by 3D scanning and patient reported outcome measures

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Context: Hormone treatment induces feminization of the body in transwomen (male assigned sex, female gender identity) and masculinization of the body in transmen (female assigned sex, male gender identity). Unfortunately, the effect of hormone treatment on facial characteristics in transwomen and transmen is still unknown.

Objective. The aim was to objectify whether hormone treatment induces facial feminization in transwomen and masculinization in transmen, and how this potential change affects satisfaction and self-esteem.

Methods: We performed a single-center cohort study in which we studied 27 transwomen and 15 transmen who started hormone treatment according to usual standard care in the Amsterdam UMC, Vrije Universiteit. 3D facial images were obtained at baseline, 3 months and 12 months. The main outcome was relative local shift of skin in millimeters.

Results: After 12 months, cheek tissue in transwomen increased with 0.50mm [95%confidence interval (CI) 0.04 to 0.96] in the x-axis and 1.08mm [95%CI:0.31 to 1.85] in the z-axis. Tissue in the jaws decreased with -0.60mm [95%CI:-1.28 to 0.08] in the x-axis and -0.18mm [95%CI -0.03 to 0.33] in the y-axis. Cheek tissue in transmen decreased with -0.45mm [95%CI:-1.00 to 0.11] in the x-axis and -0.84mm [95%CI:-1.92 to 0.25] in the z-axis. These changes already started after three months. An increase in satisfaction with the face was found in both transwomen and transmen. There were no changes in reported self-esteem.

Conclusions: Hormone treatment in transwomen induces an increase in cheek tissue and a decrease in jaw tissue. In transmen a tendency of decrease in cheek tissue and an increase jaw tissue was found. These changes suggest that hormone treatment induces facial feminization in transwomen and masculinization in transmen. Furthermore, this research shows that 3D imaging is a promising tool for the evaluation of facial changes.

28. Mortality in transgender people receiving hormone treatment: results of a nationwide cohort study

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Purpose: Gender affirming hormone treatment (HT) induce physical changes in transgender people. Whether HT results in an increased mortality is not well established yet. Therefore, we aim to study mortality in a large cohort of transgender people and compare this with a Dutch male and female reference population.

Materials and methods: All transgender people who visited the outpatient clinic of the VU University Medical Center, Amsterdam, the Netherlands, and started HT between 1996 and 2016, were included. For every transgender person, 5 age-matched control males and 5 age-matched control females were included, based on a random sample from the Dutch population. This cohort was linked to Statistics Netherlands (CBS) which registers the date and cause of death of all people who lived in the Netherlands since 1996. This database was searched up to 2017. Mortality rate (expressed as percentage) and relative risk (RR) with 95% confidence intervals (CI) were calculated for transwomen and transmen separately.

Results: In total, 2,134 transwomen (median age at start of HT 49 years, inter quartile range (IQR) 37-59 years) and 1,243 transmen (median age at start of HT 37 years, IQR 24-49 years) were included, with a mean treatment duration of 13 years (IQR 5-23) and 7 years (IQR 2-9), respectively. Of the included transwomen, 9.6% were deceased, compared with 6.0% of the age-matched control males (RR 1.7, 95%CI 1.4-1.9) and 4.8% of the age-matched control females (RR 2.1, 95%CI 1.8-2.5). The decrease rate in transmen was 2.6%, compared with 2.6% of the age-matched control males (RR 1.0, 95%CI 0.7-1.4) and 1.7% of the age-matched control females (RR 1.6, 95%CI 1.0-2.3).

Conclusion: This large nationwide cohort study showed an increased mortality in transwomen compared with both age-matched control males and females. The mortality in transmen was increased compared with age-matched control females, but not compared with age-matched control males. Upcoming analyses need to determine the cause of the deceases and whether this is different from the control males and females.

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