Session 2

DUSRA meeting 19-05-2017

Diana van Heemst (LUMC)
'Metabolic health: the brain and the periphery'

Three topics were discussed during this presentation: GH secretion in the Leiden Longevity Study (LLS), glucose metabolism in longevity, and intranasal application of insulin. *In vivo*, mutations in the insulin pathway increased longevity, and this is partially thought to be due to influences of the growth hormone upstream of insulin. Offspring of long-lived elderly from the LLS had lower growth hormone levels at rest and more regularly controlled levels in comparison to their partners. Additionally, type II diabetes incidence was lower in offspring and an oral glucose tolerance test showed lower glucose levels in offspring and faster clearance. Not only that, but a hyperinsulinemic clamp measured that in offspring more glucose is needed to counteract insulin, indicating a higher sensitivity. Insulin not only affects the body directly but also acts upon a wide range of bodily functions via the brain: it increases lipogenesis, cognitive functions and energy expenditure. Intranasal insulin addition in young test subjects showed only an increase of levels in the brain fluids and no increase in serum levels and showed a changed response after a meal or glucose was given. This changed response could be due to an increased hypothalamus activity and some response in the ventral tegmental area (VTA). Type 2 diabetes patients showed no response towards insulin in the brain.

During the discussion the audience was interested if the researchers also measured any difference in thyroid response between the offspring and partners. Diana mentioned that the thyroid-stimulating hormone (TSH) was higher in offspring but that no differences in triiodothyronine (T3) and thyroxine (T4) were measured. Another interesting point mentioned in the discussion, was whether the partners of the offspring are a good control or whether longer lived people were chosen in the sense that you choose someone compatible with your lifestyle. Diana replied to this by admitting that it could be an important factor in their research, but that the same birth cohort did not show any differences in height, suggesting that there is no large bias in the controls.

Luc van Loon (Maastricht UMC)
'Anabolic resistance of ageing'

The topic of the presentation is the physiology of the human muscle. Muscle turn-over is continuous during our life, in 2 months all the muscles in the arm are 'new'. Muscles can recondition and thereby change to conditions, however, during ageing deconditioning happens, e.g. sarcopenia. But what regulates muscle maintenance? Anabolic stimuli are better known than catabolic stimuli and they seem to drive maintenance, one example is food. The processing of food happens on many levels: protein digestion, amino acid absorption, plasma amino acid availability, hormonal response, post prandial perfusion, and myofibroblast protein synthesis.

Physical activity and electrical stimulation are known to stimulate muscle growth. It seems that a physical activity before a meal improves the uptake of protein in the muscle: "you are more of what

you eat". Immobilised muscles, e.g. with a cast, show a decrease in their capacity to take up protein. This phenomenon is especially a problem in the elderly, since the bedrest after disease or injury happens more often and because they already have anabolic resistance, it would takes them 6 months to regain the muscles they lose per week. This could result in a catabolic crisis model, where not all lost muscle is regained. Preventing muscle mass loss is therefore more important than regaining it afterwards. Part of the solution to prevent muscle loss in the elderly is to give nutritional support in combination with physical activity or electrical stimulation .

During the discussion the audience was asking questions regarding the order of exercise and food intake for better muscle maintenance. The speaker explained that fasting before exercise will not increase muscles and that eating or exercising prior to sleep does not give a huge benefit. He also elaborated on studies that demonstrated that you can stimulate muscle growth during sleep with food and electrical stimuli. The Mediterranean diet was suggested to be good for muscle maintenance due to the fact that protein retention is lower in the gut, when the diet is low in protein.

Simon Mooijaart (LUMC)
'Ageing research and the older patient; challenges and opportunities'

The topic of the presentation is older patients in the clinic. Evidence based medicine in the clinic comprises the knowledge and expertise of the physician, scientific evidence, and the situation and preferences of the patient. At the moment evidence based medicine is not present for older patients because most of the clinical trials for medication used in elderly were performed using younger and therefore a more homogenous group of individuals. Therefore this needs to be incorporated in the scientific agenda, especially given the fact that unhealthy things such a high blood pressure are bad in young patients but have been shown to increase life expectancy in the elderly. An example where this evidence based medicine is highly necessary is end stage renal disease, which is becoming more prevalent and where the treatment is very expensive. The older patients can be used as a model and as a bridge between clinical and fundamental research.

In the discussion questions were asked whether the trend to take theories on aging on board in the clinic and what generic or specific markers are for the ageing process. The speaker thought it would be interesting to look at the whole patient and incorporate this model in the clinical setting and states that more collaborations between departments are necessary. The audience asked the speaker to elaborate on the statement of the speaker that he didn't believe in vitality assessment, but wanted to go more towards a biological assessments. The speaker mentioned that there are many models and that no single screening method is the best. In his opinion it was very important to keep discussing screening with others and especially inform the patient of the percentage of risk. Because there is of course a lot of clinical data, the question was raised on the potential for international collaborations in this field. Unfortunately, there is not a very big awareness for the topic of clinical trials in the elderly, but there is a small interest by some other clinicians. The last question asked was about whether high blood pressure and high cholesterol are really good in the elderly or are part of the survival package. To which the speaker replied that these results have only come from observational data, we don't know what the blood pressure of these people was when they were younger. At the moment clinical trials are ongoing on these topics.

Anneke Den Hollander (Radboud University)
'The ageing eye: insights into the molecular pathogenesis of age-related macular degeneration'

Prevalence of Age-Related Macular Degeneration (AMD) increases with age and results in blurred vision and black holes in the centre. AMD is a common cause of vision loss in the elderly and has a strong genetic component. The hypothesis is that multiple high frequency mutations with low effect or more specific intermediate-low frequency mutations with intermediate effect are causal. Genome wide association analysis studies (GWAS) in combination with exome sequencing studies have been performed resulted in the identification of 45 common and 7 rare variants. GWAS has thought us about AMD that 1) both common and rare variants are associated and could be used in a model to asses diseases risk, 2) complement pathway, lipid metabolism and extracellular matrix are involved in AMD development and 3) new treatments targeting the complement system, but have not shown results yet. The next step is to improve the prediction models, by investigating serum and plasma biomarkers and use well designed big cohort OMICS studies to find hypothesis free predictions markers and possibly identify subgroups to facilitate patient specific treatment.

The discussion started with the question whether they saw an overlap between the biomarkers and genetic loci. Anneke told that namely the rare variants show an overlap and patients had a higher level of complement in general. A more ethical question was raised about the prediction using biomarkers and OMICs, because at the moment there are no treatments for AMD. Upon this question Anneke reflected on what they discussed last week at a big conference where 60% of the audience was against making a genetic test available for the same reason. However, as environmental factors also influence the onset of AMD, a genetic test might motivate a life style change. The influence of life style led to the question whether ADM was seen to be reversible in nutritional trials. However, only a small trial with zinc to prevent end stage ADM showed a reduced activation of the complement system and improved outcome. Anneke mentioned that the difficulty with ADM is that the vision loss is dynamic, patients might suddenly become better or worse, but it is not reversible. The final question was how an allergy can be protective against AMD, but that was not known yet but could possibly have something to do with the complement system associated with AMD.