Maastricht University

Cognition and type 2 diabetes : the interplay of risk factors

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Knowledge valorisation

Knowledge valorisation refers to the "process of creating value from knowledge, by making knowledge suitable and/or available for social (and/or economic) use, and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities" (adapted definition based on the National Valorisation Committee 2011:8).

Mr. D. is a 70-year-old man who lives together with his wife. His wife has noticed that her husband has some problems with his memory. She does not know whether these memory problems are normal for his age. She is afraid her husband is developing dementia and decides to make an appointment with their general practitioner. The general practitioner concludes that Mr. D. should be referred to a neuropsychologist and has seen in Mr.D's medical record that he is diagnosed with diabetes and hypertension for a few years. Could there be a relation between his blood pressure and diabetes and his cognitive problems? Is there a possibility for Mr.D. to prevent further cognitive decline? How could the neuropsychologist and the internist play a role in this? And how could Mr. D and his wife benefit from results of this thesis?

Societal relevance

What is the social (and/or economic) relevance of the research results (i.e. in addition to the scientific relevance)?

Nowadays almost every person in the world knows someone who suffers from dementia. Dementia is a progressive disease that is characterized by decline in mental abilities, also known as cognitive functions. Specifically, individuals with dementia suffer from decline in memory function. Decline in cognitive functions is, however, not the only symptom of dementia as patients with dementia can also suffer from behavioral problems and depression. This can lead to a large decline in quality of life and to a huge burden for caregivers, i.e. spouses or children of the patient.

Dementia is highly prevalent worldwide; In 2010 it was estimated that 35.6 million people lived with dementia and these numbers are expected to almost double every 20 years to 65.7 million in 2030 and 115.4 million in 2050. In addition, the worldwide societal economic was estimated at US $ 604 billion in 2010. These alarming numbers indicate that it is very important to find a treatment to delay or prevent the development of dementia.

However, there is still no effective treatment to significantly delay the onset of dementia. Therefore, it is important to identify risk factors for dementia that can be treated. An average five-year delay in the age of onset of dementia would tend to reduce population prevalence by 50% and thereby greatly reduce the impact of

dementia in the general population. Furthermore, recent studies have suggested that the incidence of dementia is decreasing, possibly as a result of improved control of vascular risk factors (e.g. hypertension) and cardiovascular disease. Therefore, studies are needed that examine how these risk factors can be modified and whether better control of these risk factors could indeed at least significantly delay the development of dementia.

Dementia is preceded by a phase of cognitive decline in which individuals show memory problems, but are not demented yet. This phase is particularly important, because in this phase further memory decline may be prevented. It would therefore be important to focus on risk factors for cognitive decline that may precede dementia diagnosis.

In this thesis we have identified certain modifiable risk factors, i.e. diabetes, low and high blood pressure, and high accumulation of certain proteins in tissue, called advanced glycation end-products (AGEs). This thesis stresses that individuals in whom these risk factors are present may have an increased risk of developing cognitive problems. Since adopting a healthy lifestyle can ameliorate the impact of these risk factors and can even prevent their development, it is very important that people are aware of the negative effects of these risk factors on the brain. If people start to adopt a healthy lifestyle, the prevalence of dementia may decrease dramatically.

In addition, physicians should become aware of these risk factors and should see them as “red flags” for cognitive decline. Physicians should monitor both blood pressure and blood sugar levels, and maybe in the future also the accumulation of AGEs in skin tissue, together with cognitive functioning in order to potentially delay or prevent the development of cognitive decline and dementia.

Target groups

To whom, in addition to the academic community, are your research results of interest and why?

Results of this thesis are important for all individuals. They implicate that prevention or control of diabetes and high (hyper) or low (hypo) blood pressure may prevent or delay cognitive decline. Ideally, this prevention or control should start early on in life by adopting a healthy lifestyle. Therefore, people should become aware of their risk of developing cognitive problems. Our results are particularly important for individuals who are middle-aged and have diabetes and hyper– or hypotension. These individuals should check their blood sugar levels and blood pressure and should visit their physicians regularly. As mentioned previously, physicians should follow-up their patients in whom these risk factors are present. Another target group is the pharmaceutical industry. Results of this thesis should encourage drug industries or diabetes specialists to invent new treatment or adjust their current treatments for diabetes and hypertension. New or intensified treatments that both control sugar or

blood pressure levels and prevent or delay cognitive decline would be like killing two birds with one stone. It would be particularly interesting for pharmaceutical industries to develop treatments to reduce accumulation of AGEs. This thesis shows that AGEs are related to cognitive functions and may therefore be a new target for treatment. AGEs have also been associated with dementia and with vascular disease and could therefore be a potential new promising candidate for the prevention of or delaying the development of dementia. However, more research into the effect of AGE accumulation on dementia is warranted, because this is a relatively new research area.

Not only treatment of diabetes and other vascular risk factors could potentially affect cognitive functioning, also extra education for patients in whom these risk factors are present, especially for those who may have difficulties with understanding the impact of their disease, may help to manage diabetes, blood pressure and cognitive functions. Diabetes nurses could provide this education, and these educational programs may be developed by universities or psychologists who are specialists in providing educational training.

Innovation/Products

To what degree can your results be called innovative in respect to the existing range of products, services, and processes?

The most innovative part of this thesis involves the measurement of skin autofluorescence (SAF) with a SAF reader. This reader measures fluorescence of certain AGEs (proteins that are bound to sugar) in the skin (volar side of the forearm) and this is assumed to reflect not only accumulation of AGEs in the arm, but in other parts of the body, like the brain, as well. We have shown, that this fluorescence, as a marker of tissue AGE accumulation, is associated with cognitive functions, particularly memory. The SAF reader may therefore become a tool for the risk assessment of cognitive impairment and dementia in clinical settings. However, more research is needed to examine the predictive value of this tool, especially in patient groups. Our research should be a regarded as a promising starting point for future studies, which may lead to the development of a new biomarker and non-invasive tool for the risk assessment of dementia.

Implementation

How can the results of this thesis contribute to implementation of new protocols and assessments in the clinical settings?

The clinical importance of this thesis involves the identification of certain vascular risk factors, especially type 2 diabetes, for cognitive decline. It is important for clinicians to get insight into the vascular risk profile, including diabetes status and

blood pressure, and to monitor these factors as well as cognitive performance. Better control of diabetes and blood pressure may contribute to less change in cognitive functions over time. Therefore, cognitive functioning should be included in the checklist of physicians who are specialized in metabolic disease (e.g. internists). In addition, information about vascular risk factors (blood pressure and diabetes status) should be gathered during the anamneses by a neuropsychologist/psychiatrist. This could help to identify individuals who are at increased risk for cognitive impairment and could make early intervention and treatment possible.

The assessment of AGE accumulation could also become an important point on the checklist of an internist and psychologist/psychiatrist. However, more research is needed into the predictive value of skin autofluorescence for dementia. Therefore, the SAF reader should first be used for research at memory clinics to examine whether patients with a diagnosis of Mild Cognitive Impairment (individuals with cognitive complaints which are not (yet) severe enough to be regarded as dementia) or dementia show higher SAF levels than individuals without a clinical diagnosis of cognitive impairment (those with subjective cognitive complaints).

Furthermore, larger studies should examine whether SAF can predict who will develop cognitive impairments and who will not. Therefore studies that follow up individuals for a certain amount of time (several years) are needed. If the SAF values indeed appear to predict the development of cognitive impairment, the SAF reader can be implemented in clinical settings, which will be feasible since the measurement is non-invasive and takes only three minutes to complete. The reader can then be used in addition to neuropsychological assessments, brain scans, and other biomarkers for the prediction of the development of dementia.

The ultimate goal of studying modifiable risk factors for cognitive decline and dementia will be to delay or prevent the development of dementia. Several large randomized control trials (RCT) have examined the effect of treatment of vascular risk factors on dementia and cognitive decline. Most of these studies have focused on treatment of one single vascular risk factor and the treatment of hypertension seemed to have the most promising effect. However, most studies failed to find an effect on dementia and cognitive decline, which may be due to the study design. For example, follow-up durations may have been too short and the age of the sample may have been too high. The Innovative, Midlife intervention for Dementia Deterrence (In-MINDD) is a new study that will develop and validate online tools to help physicians to assess if an individual's lifestyle supports long-term brain health. This study will generate personal strategies for adopting a brain healthy lifestyle by stimulating change in risk factors for dementia, including smoking, blood pressure, and cholesterol. Studies, like In-MINDD, hopefully increase our understanding about how to delay or prevent dementia. One of the main advantages of In-MINDD is the multifactorial approach, which is supported by the results of this thesis. These suggest that multiple vascular risk factors can increase the risk for cognitive impairment and

provide a starting point for new studies and provide relevant information for clinicians who should regard cognitive decline and dementia as multifactorial disorders. These multiple factors, which not only include diabetes and hypertension, but also, for example, depression, smoking, and cholesterol levels, should therefore all be considered when trying to increase brain health.

So, how could Mr. D. and his wife benefit from the results of this thesis?

If the recommendations of this thesis are followed, the neuropsychologist would know that Mr.D has been diagnosed with diabetes and hypertension. After a neuropsychological assessment, a skin autofluorescence measurement could be performed for research goals so hopefully in the future this assessment can contribute to dementia risk assessment. The neuropsychologist informs the internist about Mr. D's cognitive problems and tells Mr. D. that it is very important to adopt a healthy lifestyle, because this may contribute to a healthier brain. Mr. D. is referred to his internist which from now on will not only monitor his blood sugar levels and blood pressure, but will also pay attention to his cognition in cooperation with the neuropsychologist. Mr. D. will try to increase his brain health by adopting a healthier lifestyle, because he wants to do everything he can to increase his brain health.