Motor function, paratonia and glycation cross-linked in older people

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Chapter 1

General Introduction
BACKGROUND

Within the aging population, motor function decline such as reduced walking abilities and decline in activities of daily living are commonly observed 1–4. Most human physiologic systems decline during aging, independent of substantial disease effects, at an average linear loss rate of 0.34-1.28% per year between the ages of 30 and 70 years 5. Impaired motor function is a prominent characteristic of physical frailty and is associated with a wide range of adverse health consequences such as falls, disability, death, hospitalization, and institutionalization 6,7. Different mechanisms contribute to the age-related decline in motor function. One of these mechanisms that might be a factor in this decline are advanced glycation end-products (AGEs) which have been proposed as contributing to the age-related decline of the functioning of cells and tissues in normal aging.

A specific age-related disease such as dementia is frequently accompanied by motor function decline which varies between the different dementia types 8,9. This decline in motor function precedes cognitive decline and progresses gradually over years 3. In early dementia stages, intentional movements become unstructured and clumsy followed by a decline in walking abilities indicated by the shortening of step length, diminished walking velocity, and unsteadiness 10–13. In the later stages, the patient becomes wheelchair bound or even bedridden due to paratonia, a specific manifestation of impaired motor function in people experiencing dementia 14. Paratonia was already being described beginning in 1828 15, but it was not until 2006 that a consensus definition of it was established 16. Despite this, paratonia is still fairly unknown, and the pathogenesis of paratonia is not well understood. It has been shown that patients in early stage dementia with diabetes mellitus (DM) have a significantly higher risk for the development of paratonia compared to those with dementia but without DM 17. Both Alzheimer’s disease (AD) 18,19 and DM 20,21 are related to higher concentrations of AGEs, suggesting that AGEs could possibly be involved in the development of paratonia.

MOTOR FUNCTION

Motor function is defined as any movement or activity that uses motor neurons. Different motor activities derive from the coordinated activity of distributed motor networks within the central nervous system (CNS), extending via the peripheral nervous system to the musculoskeletal structures for generating movement 22. Motor impairment can be the result of damage to motor-related brain regions, and the location of the damage within CNS structures may lead to different presentations of motor function decline 3. Furthermore, motor function decline can also be caused by peripheral changes in the nervous system or skeletal muscles. Loss of skeletal muscle mass and muscle weakness is an important contributor to a decline in motor function and functional performance 23. Besides muscle
atrophy from either disease or disuse, it has been suggested that loss of muscle contractile properties may possibly be due to biomechanical changes in the connective tissues surrounding the muscle fibres (endomysium, perimysium, and epimysium). Age-related intermolecular cross-linking processes in a muscle's connective tissue leads to changes in its mechanical properties, causing loss of elasticity and increasing tissue stiffness.

PARATONIA

Paratonia is a distinctive form of hypertonia/movement stiffness that is observed in individuals experiencing dementia and has an estimated prevalence of 10% in the early stages and up to 90-100% with later stages of dementia. The severity of paratonia increases with the progression of the dementia and is associated with a further loss of functional mobility, severe contractures (see Figure 1), and pain. Due to paratonia, daily care, especially washing and dressing, becomes uncomfortable and painful. Severe paratonia, therefore, results in a substantial increase of the caretaker’s burden and a decrease of the quality of life in the advanced stages of dementia. However, in the early stages, paratonia already has a negative and significant impact on functional mobility, and this decline has been identified as a significant risk factor for falls for those with dementia.

Definition of paratonia

In 2006, the following operational definition of paratonia was established through an International Delphi procedure with known experts in the field.
“Paratonia is a form of hypertonia with an involuntary variable resistance during passive movement. The nature of paratonia may change with progression of the dementing illness, meaning that active assistance (or “mitgehen”) is more common early in the course of degenerative dementias, whilst active resistance (or “gegenhalten”) is more common later in the course of the disease. The degree of resistance varies depending on the speed of movement (e.g., a low resistance to slow movement and a high resistance to fast movement). The degree of paratonia is proportional to the amount of force applied. Paratonia increases with progression of dementia. Furthermore, the resistance to passive movement is in any direction and there is no clasp-knife phenomenon”.

This definition enables differentiation between paratonia, Parkinsonian rigidity, and spasticity after a stroke. Contrary to paratonia, Parkinsonian (lead pipe) rigidity has a constant degree of resistance that is not influenced by the speed of the movement. Furthermore, in paratonia, there are no exaggerated tendon jerks (clasp-knife phenomenon) which is in contrast with spasticity.

**Diagnosing Paratonia**

The Paratonia Assessment Instrument (PAI) is the only valid and reliable instrument for assessing the presence or absence of Paratonia. The PAI is based on successively passive mobilisation of both shoulders towards ante-flexion/retro-flexion, elbows towards flexion/extension, and combined hips/knees towards extension/flexion (Figure 2). With the participant in a sitting or supine position, the examiner begins with a slow movement of the limb after which the movement is accelerated. Paratonia is diagnosed as being present when the following five criteria are all satisfied: (1) an involuntary variable resistance; (2) a degree of resistance that varies depending on the speed of the movement (e.g., low resistance to slow movements and high resistance to fast movements); (3) resistance to passive movement in any direction; (4) no clasp-knife phenomenon; and (5) resistance in two movement directions in the same limb or in two different limbs. The severity of paratonia is then scored by using a Modified Ashworth Scale for paratonia (MAS-P). During the PAI assessment, the assessor quantifies the muscle tone based on the resistance induced by the passive movements of the limbs. The MAS-P is based on a 5-point ordinal scale ranging from 0 to 4, meaning 0 = no resistance, 1= slight resistance, 2 = more marked resistance, 3 = considerable resistance, and 4 = severe resistance such that passive movement is impossible. A score of 0.5 is assigned in the event of active assistance.

Because of the inherent characteristics of paratonia (e.g., variability in movement resistance), accurate and objective measurement of paratonia severity proves to be challenging.
Although MAS measurement is the worldwide standard for measuring the resistance to passive movements in clinical settings, extensive experience is necessary for the MAS to be reliable. An objective and accurate alternative for measuring muscle properties is available with the MyotonPRO. It is a quickly applicable, painless, and non-invasive handheld device that measures muscle properties such as tone, elasticity, stiffness, creep, and mechanical stress relaxation time, however, it still needs to be validated for people with paratonia.

ADVANCED GLYCATION END-PRODUCTS

Since the early 1980s, it has been proposed that the cross-linking of long-lived proteins mediated by advanced glycation end-products (AGEs) may contribute to the age-related decline of the functioning of cells and tissues in normal aging. AGEs formation occurs through the non-enzymatically reaction of monosaccharides with the amino groups of proteins, particularly the N-terminal amino groups and side chains of lysine and arginine. This modification, termed non-enzymatic glycosylation or the Maillard reaction, leads to a reversible, so called Schiff-base adduct. A Schiff base is a compound that has a carbon to nitrogen double bond where the nitrogen is not connected to hydrogen. The Schiff base subsequently experiences chemical rearrangement, known as the amadori rearrangement, and forms protein bound products that are more stable, or amadori products. Through subsequent oxidations and dehydrations, including free radical intermediates, a broad range of irreversible, heterogeneous, and sometimes fluorescent and yellow-brown products is formed, the so-called AGEs (figure 3). AGEs formation may also be initiated by metal-catalyzed glucose auto-oxidation and lipid peroxidation.
AGEs are spontaneously produced in human tissues as an element of normal metabolism which increases with aging and accelerates in hyperglycaemic environments. The increase of the level of free/unbound and protein bound AGEs in the blood circulation is also determined by an exogenous intake such as food. AGEs are removed from the body through enzymatic clearance and renal excretion.

Figure 3. AGE formation

With aging, there is an imbalance between the formation and natural clearance of AGEs that results in an incremental accumulation in tissues with slow turnover such as muscles, cartilage, tendons, eye lens, vascular media, and the dermis of the skin. Beside their role in AD and complications of DM, the accumulation of AGEs is a significant contributing factor in many age related diseases including renal failure, blindness, and cardiovascular diseases.

AGEs can be quantified in blood or tissue biopsies, however, due to their fluorescent properties, their presence in the skin can be noninvasively assessed using skin autofluorescence (SAF). Several types of AGEs have been described and can be categorized into fluorescent cross-linking such as Pentosidine; non-fluorescent cross-linking such as Glucosepane; fluorescent non-cross-linking such as Arginine-pyrimidine; and non-fluorescent non-cross-linking such as Carboximethyl-lysine. The cross-linking of long-lived proteins, particularly collagen, are responsible for an increasing proportion of insoluble extracellular matrix and thickening of tissue as well as increasing mechanical stiffness and loss of elasticity.

Non-cross-linking effects are exerted by the binding of AGEs to the receptor for AGEs (RAGE). RAGE is a multi-ligand member of the immunoglobulin superfamily of cell surface molecules that is widely localized in a variety of cell lines including monocytes, endothelial, mesangial, neuronal, and muscle. The interaction with AGEs incites activation of intracellular signalling, gene expression, and production of pro-inflammatory cytokines (such as

Advanced Glycation End-Products (AGEs) are irreversible damaged proteins through binding with sugars (figure 4).

Cross-linking effects:
- thickening of tissue
- increasing mechanical stiffness
- loss of elasticity

Non-cross-linking effects (by pro-inflammatory processes and oxidative stress):
- increasing mechanical stiffness
- loss of elasticity
- neural function decline
Interleukin (IL)-6, Tumor Necrosis factor (TNF)-alpha), and free radicals. At the peripheral (tissue) level, these inflammatory processes exhibit powerful proteolytic activity whereby the collagen becomes more vulnerable and tissue stiffness increases. At the central level (central nervous system), interaction between AGEs, Amyloid-beta, and hyper-phosphorylated tau-protein induce microglia and astrocytes to upregulate the production of reactive oxygen species, pro-inflammatory cytokines, and nitric oxide which affects neuronal function.

Figure 4. AGEs may form cross-links and/or adducts on collagen structures. This figure shows a collagen fibril and the formation of Glucosepane, which links Lysine and Arginine sidechains. The two amino acids can belong to separate molecules (top), forming an intermolecular cross-link, or to the same molecule (bottom).

THE AIM OF THIS THESIS

The main objective of this thesis is to study whether AGE accumulation contributes to motor dysfunction in the aging population in general and to the pathogenesis of paratonia in particular. It will be the first step in unravelling the phenomenon of paratonia on a fundamental level. Another aim is to establish an objective method for quantifying the severity of paratonia by studying the psychometric properties of the MyotonPRO, a portable device that objectively measures muscle properties.

OUTLINE OF THIS THESIS

To identify a direct relationship between AGEs and motor function decline, a systematic review was conducted. This review revealed a lack of research into the relationship of AGEs and physical activity and function within the older population, leading to a specific
investigation into this topic. The specific relationship between AGEs and paratonia and functional performance in the target group of dementia was then investigated. Finally, an easy and objective measurement tool for measuring paratonia severity was studied that could be used for further research into paratonia.

This thesis answers the following research questions;
1. Is there a direct relationship between circulating and/or tissue AGEs and motor function decline (Chapter 2)?
2. Are AGE levels associated with physical activity and physical functioning in older individuals (Chapter 3)?
3. Are AGE levels associated with the prevalence and severity of paratonia in patients with Alzheimer’s disease and mixed dementia (Chapter 4)?
4. Are AGE levels associated with a decline of functional performance in people with Alzheimer’s disease and mixed dementia (Chapter 5)?
5. Is the MyotonPRO a valid and reproducible tool for assessing paratonia severity? (Chapter 6)?
REFERENCES


