The role of inflammaging and advanced glycation end products on paratonia in patients with dementia

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Abstract Impaired motor function is a prominent characteristic of aging. Inflammatory processes and oxidative stress from advanced glycation end-products are related to impaired motor function and could plausibly be a contributing factor to the pathogenesis of paratonia, a specific motor disorder in people with dementia. Severe paratonia results in a substantial increase of a caretaker's burden and a decrease in the quality of life. The pathogenesis of paratonia is not well understood, and no effective interventions are available to combat it. Intensive glycaemic control, reducing oxidative stress, possibly combined with a low AGE diet and AGE targeting medication may be the key method for preventing advanced glycation end-product accumulation and reducing the inflammatory burden as well as possibly postponing or preventing paratonia.

Highlights:

- Inflammatory processes from AGEs are related to paratonia
- AGE induced viscoelastic changes in muscle tissue might be responsible
- Glycaemic control could possibly be an effective way to address AGE accumulation and prevent paratonia
- This new perspective on paratonia is a beginning point for further research

1. Introduction

Aging is a progressive time dependent functional decline in an organism's physiological integrity and adaptability followed by a consequent irreversible decrease in its fertility and an increase in morbidity and mortality risk (Lopez-Otin et al., 2013). With aging, motor disorders and decline in motor function are commonly observed (Arvanitakis et al., 2004; Buchman and Bennett, 2011). 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 (Hoogendijk et al., 2019). Different mechanisms contribute to the age-related decline in motor function.

With aging, there is an increase in the levels of circulating pro-inflammatory mediators that corresponds to a chronic low- grade inflammatory profile. This profile is related to the accelerated loss of muscle mass and function, so-called sarcopenia, with Interleukin (IL)-6 and Tumor Necrosis factor (TNF)-alpha as the most reported inflammatory parameters (Beyer et al., 2012). Another mechanism is that with aging there is an increase of oxidant molecules and a decrease of antioxidant defenses, resulting in oxidative stress, which is involved in age-related conditions as sarcopenia and frailty (Liguori et al., 2018).

One specific age-related disease is dementia and is a common public health concern. There are over 50 million people globally living with dementia, and this number is expected to increase to 152 million by 2050 (Alzheimer's Disease International (ADI), 2019). The most common cause of dementia is Alzheimer's disease (AD) which is usually associated with a progressive decline in cognitive function, especially memory loss. AD is characterized by amyloid plaques and neurofibrillary tangles that are present in high numbers in the grey matter of the affected brain. Inflammatory processes in the brain have emerged as a third core pathology in AD. The sustained activation of macrophages in the brain and other immune cells has been demonstrated to exacerbate both amyloid and tau pathology and may serve as a link in the pathogenesis of AD (Kinney et al., 2018).

The role of glycation in aging was first discovered by Sell et al. (Sell et al., 1992). Glycation products are grouped under the acronym AGEs (advanced glycation end-products) and have been proposed to contribute to the age-related decline of the functioning of cells and tissues in normal aging and age related diseases such as Diabetes Mellitus type II (DM) and AD (Frimat et al., 2017; Moldogazieva et al., 2019; Vicente Miranda et al., 2016). There is increasing evidence that impaired skeletal muscle function induced by AGEs contributes to motor function decline in the aging population. AGEs have a damaging effect on the biomechanical and structural muscle properties from the intramuscular upregulated inflammation that is caused by the binding of AGEs to their receptor and/or through collagen crosslinking (Drenth et al., 2018, 2016). These damaging intramuscular processes alter viscoelastic properties and increase extracellular matrix stiffness and could be involved in the typical movement stiffness in people with dementia, called paratonia.

In this narrative review, the authors provide a summary of the recent scientific evidence concerning the role of inflammaging and AGEs in the pathophysiology and progression of paratonia, a highly prevalent but often neglected muscle dysfunction in patients with dementia. Finally, the clinical implications and suggestions for follow-up research are discussed.

2. Dementia-related muscle function disorders

2.1. Paratonia

In addition to cognitive decline, dementia is associated with motor function decline which worsens with increasing severity of dementia (Scarmeas et al., 2004). It has been shown that motor decline

precedes cognitive decline, and changes in motor function have been proposed as potential clinical biomarkers to predict dementia (Dumurgier et al., 2017; Montero-Odasso et al., 2018). A common motor disorder that is observed in individuals with dementia is paratonia which is a distinctive form of hypertonia/muscle stiffness. It has an estimated prevalence of 10% in the early stages and increases up to 90-100 % in the later stages of dementia (Hobbelen et al., 2011). Paratonia is characterized by an active, unintentional resistance of the muscle against passive movement (Hobbelen et al., 2011). The severity of paratonia increases with the progression of the dementia and is associated with a further loss of functional mobility, severe contractures , and pain (Hobbelen et al., 2006). Resistance to mobilisation (i.e. by opposite muscle contraction) in paratonia is variable, especially in the early stages of dementia when paratonia can alternate between no resistance, actively assisting, and active resistance against passive movement (Beversdorf and Heilman, 1998; Hobbelen et al., 2006). Daily care, especially washing and dressing, becomes uncomfortable and painful. When it is severe, it results in a substantial increase of the caretaker's burden and a decrease in the quality of life in the advanced stages of dementia (Souren et al., 1997). 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 (Hobbelen et al., 2011).

2.2. Role of inflammation and AGEs in the pathophysiology & progression of paratonia

Glycation has deleterious effects through three main pathways; 1: AGE tissue accumulation, 2: *in situ* glycation which leads to tissue structures damage and 3: receptor (RAGE) activation which activates proinflammatory and pro-oxidative signaling pathways. Together they lead to chronic inflammation/oxidative stress, fibrosis and tissue stiffness (Frimat et al., 2017).

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, referred to as the non-enzymatic glycosylation or the Maillard reaction, leads to a reversible, so called Schiff-base adduct which is a compound that has a carbon to nitrogen double bond in which 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 are formed, the so-called AGEs (Ahmed and Thornalley, 2007; Frimat et al., 2017; Rahmadi et al., 2011). AGEs formation may also be initiated by metal-catalyzed glucose auto-oxidation and lipid peroxidation (Moldogazieva et al., 2019).

AGEs are spontaneously produced in human tissues as an element of normal metabolism that increases with aging and accelerates in hyperglycaemic environments (Ahmed and Thornalley, 2007; Monnier et al., 2005; Rahmadi et al., 2011; Uribarri et al., 2007). 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 with processed food, provided that the AGE metabolism is effective. This means that AGE receptor 1 (AGE receptor that antagonizes AGEs), and/or the glyoxalase system is capable to bind AGEs and, then, degrade and detoxify and that RAGE (this receptor drives the inflammatory and oxidant response in the cell) is not activated. It is known that AGE metabolism is deteriorated in aging and in the context of chronic and metabolic diseases (Vlassara et al., 2016, 2008). AGEs are removed from the body through enzymatic clearance and renal excretion.

With aging, there is an imbalance between the formation and natural clearance of AGEs which results in an incremental accumulation in tissues containing collagen with a slow turnover such as muscles, tendons, vascular media, and the dermis of the skin (Luevano-Contreras and Chapman-

Novakofski, 2010; Peppa et al., 2008). Beside their role in AD and complications of DM, the accumulation of AGEs is a significant contributing factor in many age related diseases including kidney and cardiovascular disease (Frimat et al., 2017).

Serum and plasma AGE measurement includes HPLC (High-Performance liquid chromatography) and ELISA (Enzyme linked immunosorbent assay). Tissue AGE concentrations can be quantified with immunohistochemical methods using antibodies. LC-MS (liquid chromatography-mass spectroscopy) is another method for the measurement of AGEs in human skin and plasma. However, due to their fluorescent properties, their presence in the skin can be noninvasively assessed using skin auto fluorescence (Senatus and Schmidt, 2017). Several types of AGEs have been described and can be categorized into fluorescent crosslinking such as Pentosidine; non-fluorescent crosslinking such as Glucosepane; fluorescent non-crosslinking such as Arginine-pyrimidine; and non-fluorescent non-crosslinking such as Carboximethyl-lysine (Da Moura Semedo et al., 2017). The crosslinking of long-lived proteins, particularly collagen, is responsible for an increasing proportion of insoluble extracellular matrix and thickening of tissue as well as increasing mechanical stiffness and loss of elasticity (Avery and Bailey, 2005; Frimat et al., 2017; Monnier et al., 2005).

Non-crosslinking 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 implication of RAGE in inflammaging is now well known. The interaction with AGEs incites activation of intracellular signaling, gene expression, and production of pro-inflammatory cytokines (such as Interleukin (IL)-6, Tumor Necrosis factor (TNF)-alpha), and oxidation (Teissier and Boulanger, 2019). At the peripheral (tissue) level, these inflammatory processes exhibit powerful proteolytic activity whereby the collagen becomes more vulnerable and tissue stiffness increases (Frimat et al., 2017). 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 (Rahmadi et al., 2011).

AGE formation and accumulation contributes to motor function decline (e.g. muscle strength loss, walking impairment) and to a consequential decline in physical activity that is suggested to increase AGE formation and accumulation (Drenth et al., 2018; Duda-Sobczak et al., 2018). High AGE levels can be considered as a catalyst for the deterioration of motor function and, in this way, a sequence of reciprocating cause and effects of elements is created that intensifies and aggravates and consequently exacerbates the situation, i.e. a vicious circle (see Figure 1). Therefore, high AGE levels can be regarded as a biomarker and risk factor for a decline in motor function that has a subsequent negative influence on age-related diseases.
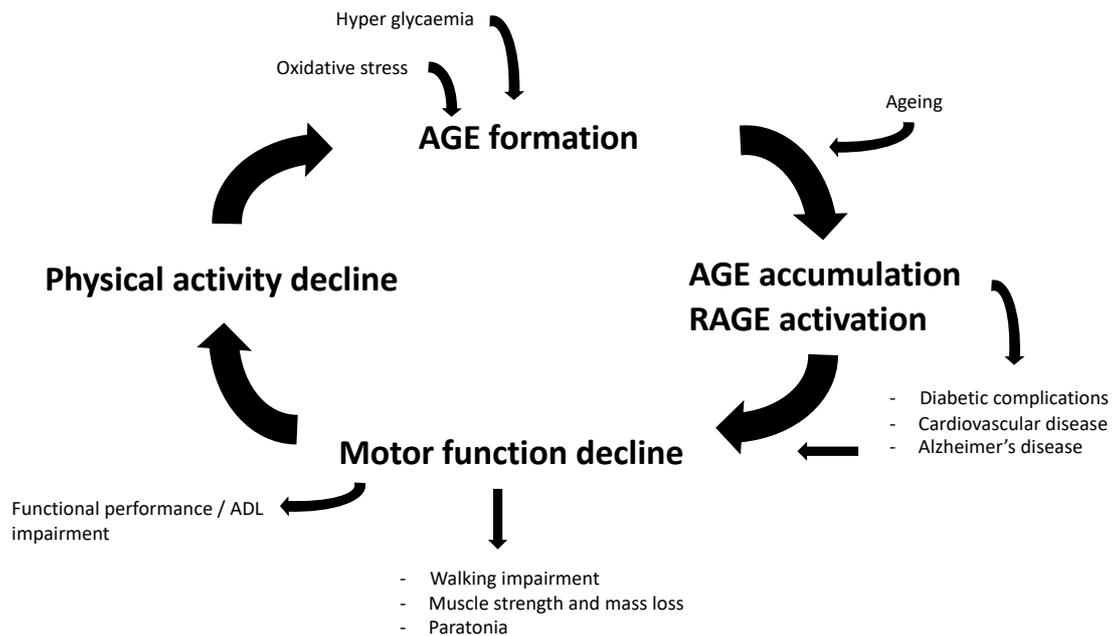
Figure 1. Vicious circle of the relationship between AGEs and motor function decline

Peripheral biomechanical changes caused by AGEs (i.e. AGE accumulation, *in situ* glycation, RAGE activation) might be partly responsible for the devastating effects of paratonia. In recent years, the authors' own research group has been focusing on early stage development of paratonia and the potential role of AGEs (Drenth et al., 2017). It has been demonstrated that patients in early stage dementia with DM have a significantly greater risk for the development of paratonia in comparison with those with dementia but without DM (Hobbelen et al., 2011). In addition, it is reported that DM is a risk factor for muscle rigidity in patients without dementia (Arvanitakis et al., 2004). Thereby, both AD and DM are related to higher concentrations of AGEs (Frimat et al., 2017; Moldogazieva et al., 2019; Rahmadi et al., 2011), suggesting that AGEs could possibly be involved in the development of paratonia. The authors found in a longitudinal study that AGE levels are associated with the presence and severity of paratonia in patients in early stage AD and mixed AD/vascular dementia (Drenth et al., 2017). It is hypothesized that the AGE induced impaired skeletal muscle function from intramuscular inflammation and/or collagen cross-linking resulting in tissue stiffness and viscoelastic changes causes the resistance perceived during passive movement in early stage paratonia (Drenth et al., 2017). It could mean, therefore, that these peripheral biomechanical changes are a factor initiating movement stiffness in the early stages whereas the central cerebral factor accelerates paratonia during the progression of the dementia (Drenth et al., 2017). Here also arises the above-described vicious circle (Figure 1) in which, as a result of the progressive dementia process, motor function becomes impaired and, as a consequence, physical activity decreases which subsequently contributes to AGE formation, accumulation and RAGE activation.

2.3. Possible therapeutic strategies

It is important to investigate whether paratonia could be postponed or movement stiffness could be improved by reducing AGE levels. Approaches to prevent AGE formation or AGE accumulation can be divided into lifestyle interventions (dietary, physical activity/exercise) and pharmacologic strategies. Pharmacological approaches to prevent AGE formation or AGE accumulation can be categorised into several classes as a function of their mechanism of action: AGE absorption inhibitors, AGE formation inhibitors, AGE cross–link breakers, RAGE antagonists, and AGE binders. Several of these pharmacological strategies with anti-AGEs effects are currently being studied, however, results show conflicting evidence (Jud and Sourij, 2019; Nenna et al., 2015). Specific circulating AGE levels correlate to dietary consumption, especially in foods that have undergone the chemical Maillard-reaction that occurs in frying, broiling, grilling, and roasting (Vlassara et al., 2016). Therefore, restricted AGEs intake is a possible factor to reduce the AGE burden in human tissues. Recent evidence describe that the consumption of a Mediterranean diet style could be a good model of low-AGE diet in both metabolic diseases and in older people (Lopez-Moreno et al., 2018, 2017, 2016). However, evidence of the harmful effects of long-term exposure to dietary AGEs are currently inconclusive (Jud and Sourij, 2019; Puyvelde et al., 2014). Regular physical exercise could also attenuate the formation and accumulation of AGEs (Ahmed and Thornalley, 2007; Couppé et al., 2014; Magalhaes et al., 2008) thereby countering the vicious circle of AGE accumulation (Figure 1). It remains unclear what physical activity should entail as well as at what frequency and at what intensity level they should be done to optimally reduce AGE accumulation. It is, therefore, important that future research examines the modalities of physical activity and exercises that significantly reduce AGE levels in the aging population in general and specifically for people with dementia. This may include low or high intensity strength and/or endurance exercises or perhaps simple, everyday physical activities. Knowledge about the content of the physical activity would help to provide specific, customized advice and exercises. This is especially important because combating central AGE accumulation may require different exercise modalities than combating peripheral AGE accumulation. Even crosslinking AGEs may require a different approach than non-crosslinking AGEs.

The glycation process is accelerated by the excessive elevation of glucose concentration and oxidative stress. Eliminating these accelerators through intensive glycaemic control and reducing oxidative stress may be the key method for preventing AGEs accumulation. Glucose concentrations can be reduced with a balanced diet while physical activity has a profound impact on glucose metabolism and oxidative stress and, therefore, could possibly reduce AGE formation (Cartee et al., 2016; Magalhaes et al., 2008). Intensive glycaemic control with a combined approach of dietary and physical exercise (and, for patients with DM, possibly in combination with medication) might be the most effective way of targeting AGE formation and thereby postponing or preventing paratonia.

3. Discussion & conclusions

Glycation, the spontaneous non-enzymatic reaction of sugars with proteins and lipids that results in AGEs is a topic of increasing importance in human health. There is increasing evidence that inflammatory processes from AGEs play an important role in aging, age-related diseases and motor function decline. Moreover, in the development of paratonia, the inflammatory processes due to an increased AGE accumulation in AD and DM appear to play a pivotal role.

Considering the mutual inter-relationship between the different structures involved in generating movement, the AGE induced damage can relate to these structures individually or even simultaneously. Therefore, besides the peripheral effect on musculoskeletal structures, AGE induced damage on peripheral neural structures could also contribute to impaired motor function by

hampering neuro-muscular and/or sensory signalling processes. It also has to be considered that AGE accumulation in the central nervous system (CNS) may affect motor function. AGE accumulation in specific relevant motor-related brain regions might have an effect on the complex inter-relationship between the motor networks within the CNS for generating movement (Drenth et al., 2016). It is even conceivable that the effect of AGEs on both central and peripheral tissue levels might even augment the decline in motor function. Future research is necessary to study this in depth.

Although the central factor, i.e., the cerebral damage caused by the dementia process, appears to be the most obvious cause of paratonia in the late stages of dementia, there is still only minimal insight into these central mechanisms on paratonia. Severe paratonia, as evidenced by high resistance during movement or active opposition, is especially seen in the later stages of dementia. In these severe stages of dementia, paratonia has been associated with the return of primitive neonatal reflexes (Damasceno et al., 2005; O'Keeffe et al., 1996; Souren et al., 1997). Additionally, clinicians and caregivers who deal in daily practice with patients suffering from paratonia have observed that movement stiffness and active opposition during ADL can vary and may occur at random moments. Factors such as aggression, agitation, anxiety, pain, and confusion but also sudden external stimuli (e.g., light, sound) are noticed as influencing paratonia. AGEs may possibly be involved in the central factor causing it because interaction between AGEs, Amyloid-beta, and tau-protein have been described to affect neuronal function (Rahmadi et al., 2011). When these neuronal functions are affected in motor function related areas, they may possibly contribute to the pathogenesis of paratonia.

In conclusion, inflammatory processes from AGEs might be a contributing factor to the pathogenesis of paratonia, a form of movement stiffness in people with dementia. Therefore, targeting AGE accumulation is imperative. This provides a new perspective on paratonia and is a beginning point for further research into the relationship between AGEs and paratonia in order to maintain longer independence for people with dementia and improve quality of life and daily care of patients suffering from paratonia.

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