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White Matter Lesions, Carotid and Coronary Atherosclerosis in Late-Onset Depression and Healthy Controls

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Background: *Cerebral white matter lesions (WMLs) are more common in individuals with late-onset or late-life depression. It has been proposed that carotid atherosclerosis may predispose to WMLs by inducing cerebral hypoperfusion. This hemodynamic effect of carotid atherosclerosis could be important for the formation of WMLs in depression.* **Methods:** *The case-control study included 29 patients with late-onset major depressive disorder and 27 controls matched for sex, age, and tobacco use. WML volume, carotid intima-media thickness, and coronary plaque volume were assessed using magnetic resonance imaging, ultrasound scan, and coronary computed tomography (CT) angiography, respectively.* **Results:** *The mean age for the total sample was 59.7 ± 4.7 years. There was no difference in carotid intima-media thickness between patients and controls ($p = 0.164$), whereas a higher WML volume in the patients was found ($p = 0.051$). In both patients and controls, WML volume was associated with carotid but not with coronary atherosclerosis. In adjusted multiple linear regression, a 0.1 mm increase in averaged carotid intima-media thickness was associated with a 52% (95% CI: 8.4–112, $p = 0.032$) increase in WML volume. The association between carotid intima-media thickness and WML volume was, however, similar in patients and controls.* **Conclusions:** *In older persons aged between 50 and 70 years, WMLs do not seem to be a part of generalized atherosclerotic disease, but seem to be dependent on atherosclerosis in the carotid arteries. Carotid atherosclerosis, however, could not explain the higher WML load observed in the depressed patients, and thus, studies are needed to establish the mechanisms linking depression and WMLs.*

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Ethical approval and patient consent: The study was approved by the Regional Scientific Ethical Committee for Central Denmark (M-20080211) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

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INTRODUCTION

The pathophysiology of depression is complex and implicates mechanisms involved in vascular disease, especially in so-called late-onset depression. Correspondingly, depression is associated with carotid atherosclerosis,[1,2] which is again associated with cerebral white matter lesions (WMLs).[3–5] Yet, the relationship between WMLs and carotid atherosclerosis in depressed cohorts has only been sparsely studied, and the results have been inconsistent.[1,2]

WMLs are focal or confluent areas in the cerebral white matter that display high signal intensity on T2- and proton density–weighted magnetic resonance imaging (MRI). The hyperintense areas correspond to varying degrees of reduced myelin content and tissue damage that are generally thought to be a consequence of small vessel disease involving ischemia, arteriosclerosis, and mild inflammation.[6]

Depression and atherosclerosis are common and important health problems in older people. Therefore, depression in the elderly or, as it is often termed, late-life depression has been extensively studied. *Late*-life depression does not take into account the age of onset of the disease, so in contemporary research, it is also common to distinguish between early-onset and late-onset depression. The age cutoff used to define these subgroups varies but is typically somewhere between 50 and 70 years. In 2 meta-analyses, it has been concluded that WMLs are more common in individuals with late-onset or late-life depression than in healthy controls.[7,8] On one hand, WMLs may lead to mood disorders, as it has been shown that WML progression predicts incident depression[9] and poorer depression outcomes[10] and that depression severity correlates with the tract-specific localization of WMLs.[11] On the contrary, depression may affect WML progression through behavioral or genetic mechanisms, hypothalamic-pituitary-adrenal-axis dysregulation, vascular endothelial dysfunction, or autonomic dysregulation, which have all been observed in depression.[12] Overall, as previously described by Santos et al.,[13] evidence points to a bidirectional relationship between depression and WMLs.

Carotid intima-media thickness (CIMT), a marker of subclinical atherosclerosis in the carotid arteries, is associated with WMLs.[3–5] It has been proposed by Shu et al.[5] that carotid atherosclerosis may lead to the development of WMLs by inducing cerebral hypoperfusion. Cerebral hypoperfusion caused by carotid atherosclerosis may be explained by decreased compliance of the carotid artery wall that leads to a higher pulsatile pressure in the cerebral vasculature and, in response, adaptive vascular remodeling inducing hypotensive conditions and localized brain tissue ischemia.[14,15] This feasible hemodynamic effect of carotid atherosclerosis could be an important mechanism behind WMLs in depression, not the least because patients with late-onset[16] and late-life depression[17] show signs of increased arterial stiffness.

Aiming to substantiate the proposal that carotid atherosclerosis leads to the development of WMLs, we hypothesized that WMLs are associated with CIMT but not with atherosclerosis in another vascular territory as represented by the total coronary plaque volume. Furthermore, we hypothesized that the association between WMLs and CIMT is different in patients with late-onset major depressive disorder when compared with controls.

MATERIAL AND METHODS

This case-control study was performed from September 2009–November 2011. The patient group ($n = 29$) consisted of 26 inpatients recruited from a psychiatric hospital (Aarhus University Hospital, Risskov, Denmark) and 3 outpatients from private psychiatric practices. The healthy controls were recruited through announcements in local newspapers and were matched to patients according to sex, age, and tobacco use (previous or current vs no tobacco use). All participants were Whites aged 50–70 years. Patients were eligible for study inclusion if they fulfilled the criteria for major depressive disorder according to The International Classification of Diseases, Tenth Revision and had no history of depression before the age of 50. Controls were eligible if they were without any history of mental disorders according to the International Classification of Diseases, Tenth Revision. Exclusion criteria were imminent suicide intent, ongoing compulsory treatment, a history of head trauma causing