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Systematic Review **Open Access**

Association between High Sensitivity C-Reactive Protein (hs-CRP) Levels and Cognitive Impairment in Elderly Patient with Type 2 Diabetes Mellitus: A Systematic Review

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ABSTRACT

Background: *HER2-positive breast cancer (BC) is known for its aggressive behavior and increased risk of brain metastases (BM), which worsens patient prognosis and limits therapeutic options due to the blood brain barrier (BBB). This study systematically evaluates HER2 overexpression as a predictive factor of BM in breast cancer patients through a Systematic Literature Review (SLR) and visualizes global research trends using VOSviewer. This systematic review assessed the relationship between serum hs-CRP levels and cognitive impairment in elderly T2DM patients, exploring its potential as an early screening biomarker.*

Methods: *This systematic review was conducted in accordance with the PRISMA 2020 guidelines. PubMed, Scopus, and Google Scholar were systematically searched for studies published between January 2017 and March 2025. Observational studies involving patients aged ≥60 years with T2DM that reported both hs-CRP levels and cognitive outcomes were included. Study selection, data extraction, and methodological quality assessment using the Joanna Briggs Institute (JBI) critical appraisal tool were performed independently by two reviewers. Due to heterogeneity in study design, cognitive assessment tools, and hs-CRP reporting, findings were synthesized narratively.*

Results: *Most studies showed that higher hs-CRP levels were associated with mild cognitive impairment and poorer executive or memory function in elderly T2DM patients. Some evidence indicated that hs-CRP elevation may precede measurable cognitive decline, suggesting its role in early neuroinflammation.*

Conclusion: *Elevated hs-CRP is consistently linked to cognitive dysfunction in elderly T2DM patients and may serve as a practical biomarker for early detection. Further longitudinal and interventional studies are needed to establish causality and diagnostic thresholds.*

Keywords: *hs-CRP; cognitive impairment; type 2 diabetes mellitus; elderly; inflammation; PRISMA 2020; systematic review*

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INTRODUCTION

Indonesia's life expectancy continues to rise annually. In 2022, the life expectancy for males reached 69.93 years and for females 73.83 years. By 2024, this figure increased to 70.32 years (males) and 74.21 years (females).[1] This demographic shift has resulted in an increasing number of elderly individuals. The elderly, defined as individuals aged over 60, naturally experience a decline in physiological function due to accumulated cellular and molecular damage.[2] Consequently, the elderly are more vulnerable to various health conditions categorized as geriatric syndromes, including frailty, delirium, urinary incontinence, and pressure ulcers.[3]

Chronic diseases such as diabetes mellitus exacerbate the risk of geriatric syndromes. Diabetes accelerates aging through the accumulation of advanced glycation end-products (AGEs), markers of tissue aging. This, combined with long-term microvascular and macrovascular complications, leads to increased incidence among the elderly. These complications directly contribute to cognitive decline, potentially due to reduced cerebral blood supply and chronic inflammatory processes.[4]

One potential inflammatory marker for detecting cognitive dysfunction is hs-CRP. Several studies report elevated hs-CRP levels in individuals with cognitive impairment and dementia. Chronic peripheral inflammation may extend to the central nervous system as hs-CRP can penetrate the blood-brain barrier. Additionally, increased CRP levels have been found in cerebrospinal fluid.[5] This systematic review aims to explore the relationship between serum hs-CRP levels and the risk of cognitive dysfunction in elderly individuals with T2DM. The study also aims to evaluate the relevance of hs-CRP as an early detection or screening tool for cognitive decline in high-risk populations.

METHODS

Study Design

This study was designed as a systematic review with narrative synthesis and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines.

Search Strategy

Relevant studies published between January 2017 and March 2025 were retrieved from three major databases: PubMed, Scopus, and Google Scholar. The following search terms and Boolean

operators were applied: ("high-sensitivity C-reactive protein" OR "hs-CRP") AND ("cognitive impairment" OR "mild cognitive impairment" OR "dementia") AND ("type 2 diabetes mellitus" OR "T2DM") AND ("elderly" OR "older adults"). Manual searches of reference lists from included studies were also performed to identify additional relevant publications.

Eligibility Criteria

Eligible studies were original observational research (cross-sectional, cohort, or case–control) that examined the association between hs-CRP levels and cognitive function in elderly patients (≥60 years) with T2DM. Only full-text articles published in English or Indonesian were included. Review articles, meta-analyses, conference abstracts, case reports, animal studies, studies involving non-diabetic or non-elderly populations, and non–peer-reviewed manuscripts were excluded.

Study Selection

All retrieved articles were imported into a citation manager and screened in two phases: title/abstract screening and full-text review. Two independent reviewers conducted the selection process, and disagreements were resolved through discussion or consultation with a third reviewer. The overall selection process was summarized using a PRISMA flow diagram, showing the number of records identified, screened, and included.

Data Extraction

Data extraction was conducted independently by two reviewers using a standardized data extraction form to ensure consistency and accuracy. From each eligible study, relevant information was systematically collected, including the authors' names, year of publication, and country of origin, as well as the study design and sample size. Detailed participant characteristics were extracted, such as mean age, sex distribution, and duration of type 2 diabetes mellitus. Information regarding hs-CRP assessment, including the measurement methods and reported cut-off values, was recorded. Cognitive evaluation methods employed in each study, such as the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), or other validated instruments, were also documented. In addition, the principal findings describing the association between hs-CRP levels and cognitive outcomes were extracted for qualitative synthesis. Any discrepancies in the extracted data were resolved through discussion to reach consensus.

Quality Assessment

The Joanna Briggs Institute (JBI) critical appraisal tool was used to assess the methodological quality and risk of bias of the included studies. Studies scoring below 60% were excluded from the synthesis. Any disagreements between reviewers were resolved through consensus. All seven included studies achieved JBI scores of ≥60% and were therefore considered methodologically adequate for qualitative synthesis.

Data Synthesis

Given the heterogeneity across study designs, populations, and outcome measures, a narrative synthesis approach was adopted. Findings were grouped according to study design and cognitive domains affected (e.g., memory, executive function, global cognition). Patterns and trends in hs-CRP–related cognitive impairment were summarized descriptively.

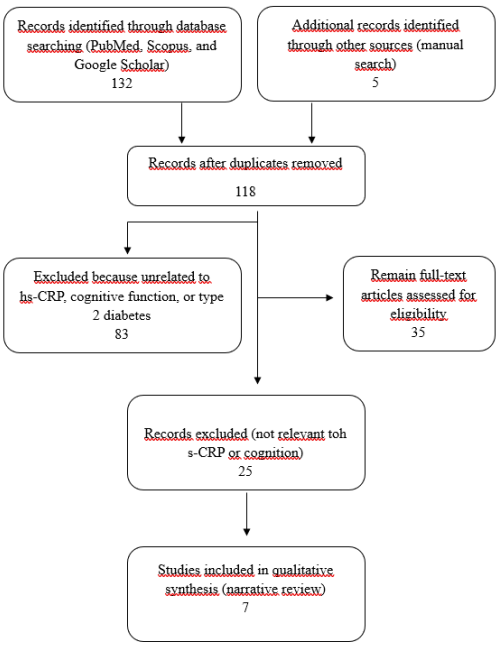

Figure 1. PRISMA 2020 Flow Diagram

A total of 132 records were identified through database searching (PubMed, Scopus, and Google Scholar) and five additional articles were found through manual reference checking. After removing duplicates, 118 records remained for screening. Based on title and abstract review, 83 studies were excluded because they were unrelated to hs-CRP, cognitive function, or type 2 diabetes.

The remaining 35 full-text articles were assessed for eligibility. Among them, 25 studies were excluded because they did not meet the inclusion criteria (non-elderly samples, non-diabetic populations, or lacking cognitive outcome data). Finally, seven studies met all inclusion criteria and

were included in the qualitative synthesis. These included studies form the basis of the present review (see Table 1 for details).

RESULTS

A total of seven studies met the inclusion criteria and were included in the final qualitative synthesis. The characteristics and findings of these studies are summarized below.

Table 1. Summary of Included Studies Evaluating hs-CRP and Cognitive Impairment in Elderly Patients with Type 2 Diabetes Mellitus

No	Author (Year)	Country	Study Design	Sample (n)	Mean Age (years)	Cognitive Test	Main Findings
1	Gorska-Ciebiada & Ciebiada (2020)	Poland	Cross-sectional	120	67.4	MMSE	Higher hs-CRP significantly associated with mild cognitive impairment (MCI).
2	Wang et al. (2023)	China	Cohort	8,540	68.3	MoCA	Elevated hs-CRP linked to faster cognitive decline over 5 years.
3	Ragaa et al. (2023)	Egypt	Cross-sectional	98	65.1	MMSE	hs-CRP correlated with executive dysfunction and

							poor memory in diabetic elderly.
4	Dwipayana et al. (2017)	Indonesia	Cross-sectional	86	63.5	—	Patients on insulin therapy had higher hs-CRP compared to oral drug users.
5	Muhammad et al. (2022)	Indonesia	Cross-sectional	150	65.0	—	Higher hs-CRP observed among elderly with chronic metabolic diseases including diabetes.
6	Banait et al. (2022)	India	Review	—	—	—	Inflammation contributing to cognitive aging.
7	Rahmawati & Laksmidewi (2021)	Indonesia	Review	—	—	—	Literature confirms hs-CRP as an inflammatory mediator associated with cognitive dysfunction in T2DM.

Across these seven studies, elevated hs-CRP levels were consistently correlated with poorer cognitive outcomes, particularly in executive and memory domains. The findings reinforce the role of systemic inflammation in neurodegeneration among elderly individuals with type 2 diabetes mellitus.

Aging Process

Elderly individuals (≥60 years) experience a progressive decline in physical function, adaptability, and increased susceptibility to degenerative diseases.[2] The aging process occurs at multiple levels: cellular, tissue, organ, and systemic. The pathophysiology of aging includes nuclear and mitochondrial DNA damage, age-related epigenetic changes, cell cycle disruption, reactive oxygen species (ROS) formation, mitochondrial dysfunction, protein homeostasis imbalance, signaling pathway alterations, and dysregulation of autophagy and metabolism.[5]

Cellular senescence is characterized by irreversible cell cycle arrest, resistance to apoptosis, inflammation, and tissue damage. The accumulation of senescent cells contributes to pathogenesis in degenerative conditions, leading to chronic inflammation, metabolic dysregulation, stem cell dysfunction, chronic diseases, geriatric syndromes, and decreased immunity.[5] This cellular-level damage progresses to organ system decline, including the nervous, digestive, cardiovascular, and respiratory systems. Body composition changes also occur, such as reduced muscle mass, increased fat mass and centralization, and elevated intramuscular fat.[6]

Cognitive Impairment

Cognitive impairment is commonly divided into non-dementia cognitive impairment or mild cognitive impairment (MCI), and dementia. MCI is defined as a decline of 1–1.5 standard deviations below the age-appropriate mean in one or more cognitive domains, without significant interference in daily functioning, representing a transitional stage between normal aging and pathological decline.[7] Dementia involves impairment in one or more cognitive domains with associated deficits in daily living and social functioning. MCI is prevalent in 10–20% of elderly individuals over 65 without dementia, with risk of progression to dementia at 10–15% annually, and up to 80% over six years.[7] Studies such as the Mayo Clinic Study of Aging and the American Academy of Neurology estimate MCI prevalence at 15–20% in individuals aged >65.[8]

Brain function progressively declines with age, mainly affecting learning and memory. These processes rely on synaptic plasticity involving the hippocampus and cortex, and recent studies show the cerebellum also plays an independent role. Neuronal and non-neuronal cells such as astrocytes undergo

senescence during aging. Astrocytic metabolic changes can disrupt neuronal metabolism, ultimately affecting neural function and reducing biosynthetic capacity with age.[9,10]

Cognitive impairment progresses from MCI to dementia, driven by structural and functional brain changes due to aging, and lifetime risk factors such as hypertension, diabetes, dyslipidemia, malnutrition, and cerebrovascular disease.[11] Hippocampal atrophy impairs memory, and persistent damage becomes irreversible. Cognitive decline includes deteriorating thinking, concentration, intelligence, memory, and language, as well as visuospatial and executive functions. β-amyloid plaques and neuronal shrinkage, synapse loss, and white matter changes are frequently found in affected individuals.[12]

Cognitive Function Assessment

Screening tools for cognitive function in the elderly are critical for detecting cognitive impairment. Early identification helps prevent dementia, which affects quality of life.[13] The gold standard for diagnosing cognitive impairment is neuropsychological testing, which is time-intensive and requires trained physician to conduct. Common screening tools include the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Ascertainment Dementia 8 (AD8), Clock Drawing Test (CDT), and CERAD.[7]

Montreal Cognitive Assessment (MoCA)

MoCA is a brief screening tool for MCI, evaluating attention, concentration, calculations, executive functions, memory, language, visuospatial skills, conceptual thinking, and orientation in approximately 10 minutes. The Indonesian version (MoCA-Ina) has been validated, with a maximum score of 30; scores ≥26 are considered normal, while ≤25 indicates cognitive impairment. One additional point is given to individuals with ≤12 years of education if the score is below 30. MoCA has superior sensitivity for detecting MCI.[14,15]

Mini-Mental State Examination (MMSE)

MMSE is better suited for detecting moderate to severe cognitive impairment, assessing general cognitive function. Interpretation considers education and awareness levels. MMSE score categories include: 0–16 (severe impairment), 17–23 (moderate impairment), 24–30 (normal cognition).[15]

DISCUSSION

This review synthesized findings from seven studies that examined the relationship between hs-CRP and cognitive impairment in elderly individuals with type 2 diabetes mellitus. Collectively, these studies support the hypothesis that chronic systemic inflammation, reflected by elevated hs-CRP levels, contributes to neurodegenerative changes and cognitive decline.

Diabetes Mellitus and Cognitive Impairment

Diabetes is a major risk factor for cognitive impairment, with incidence doubled in T2DM patients compared to healthy individuals.[16] Global studies—including the Health and Retirement Study (HRS), Mexican Health and Aging Study (MHAS), and Brazilian Longitudinal Study of Aging (ELSI-Brazil)—demonstrate increased cognitive impairment in diabetes patients. Meta-analysis show a 62% higher risk of cognitive decline and dementia, with diabetes associated with 1.5 times greater risk of Alzheimer's and 2.5 times higher risk of vascular dementia.[17] A U.S. cohort study found elevated blood glucose levels to be a risk factor for dementia even in non-diabetes patients.[18]

In elderly population living with diabetes, cognitive impairment is influenced by disease progression, poor glycemic control, comorbidities, and complications. The exact mechanisms remain unclear, but high HbA1c, recurrent hypoglycemia, and glucose instability have been linked to cognitive dysfunction.[14] Studies by Underwood et al. (2024) show prolonged disease and use of hypoglycemic drugs, like insulin increase cognitive risk.[19]

Hyperglycemia plays a central role in cognitive decline in T2DM through amyloid metabolism disruption, microvascular damage, insulin dysregulation, IGF-1 signaling changes, and inflammatory cytokine elevation.[16,17] These factors directly impair neural tissue or cause vascular changes leading to cerebral infarct. Insulin supports neuronal growth and protection, but peripheral insulin resistance may reduce brain insulin, impairing cognition. [18] T2DM alters neuronal metabolism, vascular systems, and support tissues, primarily via insulin resistance, hyperglycemia, and inflammation. Insulin resistance disrupts neuronal energy, antioxidant balance, and promotes amyloid-β accumulation, triggering inflammation and blood-brain barrier damage.[20–22] Chronic hyperglycemia increases AGEs, damaging neurons critical for cognition. MRI findings such as hippocampal atrophy, white matter hyperintensities,

and microvascular changes support these effects.[23] The accumulation of advanced glycation end-products (AGEs), toxic lipid by-products, and proteins from these processes leads to endothelial damage, increased production of reactive oxygen species (ROS), and reduced production of vasodilatory substances. Endothelial damage also triggers the release of inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[24]

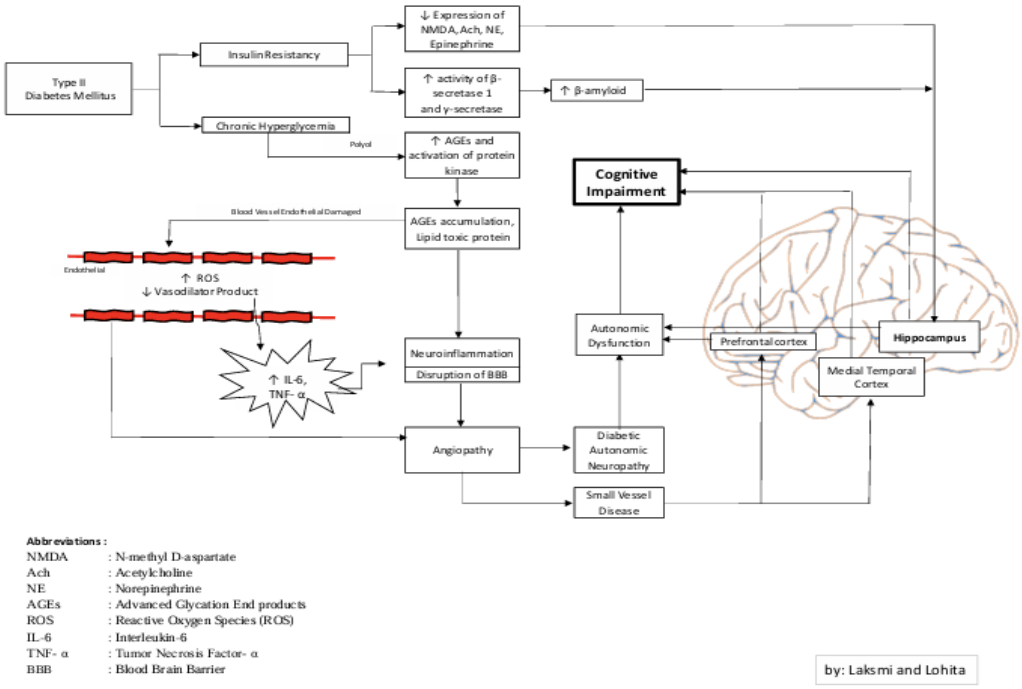

Figure 2. Patophysiology of cognitive impairment in DM type 2 [24]

The development of cognitive impairment in patients with type 2 diabetes mellitus results from a complex interplay of various factors, including those affecting brain structure and cognitive function as described in the previous section. Structural changes in the brains of patients with type 2 diabetes mellitus may include a decrease in hippocampal volume, reduced gray matter in the medial temporal area, anterior cingulate, and medial parts of the frontal lobe, and/or reduced white matter in the frontal and temporal regions.

Microstructural changes in the brain's white matter in type 2 diabetes mellitus can disrupt connectivity between different brain regions, thereby impairing cognitive functions. These changes may include lacunar infarcts, white matter hyperintensities, and cerebral microbleeds, collectively referred to as small vessel disease. [24]

High-Sensitivity C-Reactive Protein (hs-CRP)

C-Reactive Protein (CRP) is a blood protein that binds to C-polysaccharide and forms a 120 kDa pentamer. Normally low, CRP levels rise 100–200 fold during systemic inflammation with endothelial damage.[25] Inflammatory processes contribute significantly to cognitive dysfunction in diabetes, potentially driven by insulin resistance-related cellular inflammation.[26] Ultrasensitive ELISA methods have enabled hs-CRP measurements. Though CRP and hs-CRP are the same molecule, hs-CRP has greater analytical sensitivity, allowing it to detect low-grade chronic inflammation.[27] According to CDC guidelines, hs-CRP >3 mg/L indicates high vascular disease risk.[25] Elevated hs-CRP has been observed in acute ischemic stroke, epilepsy, hypertension, chronic kidney disease, cancer, and obesity.[28]

CRP is a mild inflammation marker linked to T2DM complications. It activates immune cascades and neurodegeneration through complement system activation. In T2DM, intracellular hyperglycemia damages mitochondria and increases oxidative stress via ROS, leading to macro- and microvascular damage. Pro-inflammatory gene expression and cytokines cause hepatic CRP synthesis.[29,30]

Decreasing hs-CRP levels has proven effective in controlling diabetic complications, and hs-CRP can detect prediabetes.[31] High hs-CRP correlates with reduced cerebral vasoreactivity and vasodilation, impairing executive and cognitive functions. In elderly with T2DM patients, high hs-CRP levels associate with MCI and elevated HbA1c.[24] Even in diabetes patients without MCI, rising hs-CRP may be a signal of early MCI development. Studies confirm a significant relationship between hs-CRP and MCI, particularly in attention and executive function domains.[30]

CONCLUSION

The rising life expectancy in Indonesia results in an increased elderly population, prone to geriatric syndromes due to cellular, tissue, and organ aging. Cognitive impairment is a common manifestation, exacerbated by chronic conditions such as T2DM through low-grade systemic inflammation. High-sensitivity C-reactive protein (hs-CRP) serves as a potential biomarker for early identification of cognitive impairment. Studies support its association with cognitive impairment and suggest its use as a screening tool, together with neurocognitive assessments like MoCA and MMSE.

Conflicts of Interest

There was no conflict of interest.

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Aknowledgments

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