Arh. farm. 2026; 76: 55 – 80 *Review article/Pregledni rad*

Microglial Dysfunction and Cognitive Impairment in Animal Models of Diabetes Type 2: A Systematic Review Bridging Diabetes and Early-Stage Neurodegeneration

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Received: 09 February 2026; Revised in revised forme: 11 March 2026; Accepted: 11 March 2026

Abstract

Diabetes Type 2 (T2D) is closely associated with cognitive impairment and an increased risk of dementia. Early neuropathological alterations in T2D are increasingly considered to involve neuroinflammatory processes, suggesting that microglial function in the diabetic brain may be compromised or shifted towards a maladaptive activated state. Growing evidence implicates microglial dysfunction as a key mechanism underlying T2D-related cognitive impairment. Alterations in spatial learning, memory, and executive function are accompanied by functional and phenotypic changes in microglial cells, particularly within hippocampal and cortical circuits. At the same time, early neurodegenerative changes occur, including neuronal loss, synaptic alterations, accumulation of Aβ and p-Tau, and Alzheimer's disease (AD)-related transcriptomic signatures in vulnerable brain regions. With aging, microglia contribute more significantly to neurodegeneration as their regulatory interactions with neurons weaken, favoring sustained activation. This mini systematic review aims to synthesize current *in vivo* evidence on the relationship between cognitive impairment and microglial alterations in animal models of T2D and to delineate the underlying pathophysiological mechanisms linking chronic metabolic stress, microglial dysfunction, and early neurodegenerative changes. Furthermore, it seeks to highlight how these mechanistic pathways, encompassing microglial signaling, inflammatory mediators

and metabolic reprogramming, may represent promising therapeutic targets for preventing or attenuating diabetes-associated neurodegeneration.

Key words: diabetes type 2, animal models, cognitive impairment, microglia, neurodegeneration

https://doi.org/10.5937/arhfarm76-64833

Introduction

Diabetes Type 2 (T2D) is dominantly prevalent in older adults and is increasingly recognized as a driver of accelerated brain aging and increased dementia risk (1). Experimental and clinical data indicate that chronic metabolic stress in T2D exacerbates age-related vulnerability of neural circuits, particularly in hippocampal and cortico-limbic networks (2). One of the earliest brain changes proposed in T2D is neuroinflammation, suggesting that microglial function may be impaired or maladaptively activated in the diabetic brain (3). Over the past decade, emerging *in vivo* studies have directly linked T2D-induced cognitive impairment to microglial alterations, including changes in microglial number, morphology, and phenotype (4–6). Therefore, the aim of this mini systematic review was to summarize the current state of knowledge and identify gaps regarding cognitive decline in T2D and microglial function with taking into account preclinical studies which assessed both domains: cognitive and microglia-related.

Methodology

In this mini-systematic review, we focused on *in vivo* studies using animal models of T2D that assessed both cognitive performance and microglial status in the brain, similarly as in previous study (7). Specifically, we used the following search terms: (“cognition” OR “memory”) AND “diabetes” AND “type 2” AND “microglia” in PubMed database. This search was performed on January 29, 2026, and yielded 76 potentially relevant publications since 2011. We excluded review articles (7 publications) and studies focused on the interaction of T2D with other comorbidities, such as AD in AD-related models or in models of cardiovascular diseases. We also excluded studies that evaluated microglial effects *in vitro*. Unfortunately, some potentially relevant studies had only abstracts available, or the manuscript was available only in Chinese, so they were excluded from this review (8 publications). After excluding studies that did not meet our eligibility criteria or were not available, we retained 27 articles that investigated microglial involvement in cognition in adult T2D models. For each eligible study, we extracted data on animal strain, age, sex, diabetes model and/or diabetes induction procedure, and the specific behavioral tests used to evaluate cognition and the results obtained in them. Moreover, we collected information on microglial outcomes, including cell density, morphology, polarization and/or phenotype markers, and/or associated cytokine profiles. All extracted data were organized and synthesized in the main summary table – Table I. In addition, we were focused to identify how often sex was included as a biological variable and at which age stage each study was conducted to evaluate possible aging effects (8).

Table I Summary of the systematic review aimed to identify the effects of preclinical models of diabetes type 2 on various cognitive tests and microglial function in the context of age and sex; Abbreviations: high-fat diet (HFD), interleukin (IL), tumor necrosis factor (TNF)-α

Tabela I Sadržaj sistematskog pregleda usmerenog na ispitivanje efekata prekliničkih modela dijabetesa tipa 2 na različite kognitivne testove i funkciju mikroglije u kontekstu uzrasta i pola; Skraćenice: dijeta sa visokim sadržajem masti (HFD), interleukin (IL), faktor nekroze tumora (TNF)-α

Number	Behavioral test	Animals	Age (at experiment initiation unless otherwise specified)	Sex	Diabetes model	Behavioral change	Microglial change	Reference
1	MWM	C57BL/6 mice	7 weeks	Unknown	Type 2; high-fat, high-sugar diet (33.6 % chow, 8 % sucrose, 26 % lard, plus protein, milk powder, minerals, fiber, and micronutrients) and streptozotocin at 40 mg/kg i.p. once daily for three days	Impaired spatial learning in T2D vs controls.	Increased expression of CD86 and decreased expression of CD206 when co-labeled with IBA-1 in T2DM group mice vs controls. M1 polarization triggered; increased number of microglia in the cortex; M1 marker iNOS expression increased in T2D model vs controls; increased IL-6 and TNF-α and decreased Arg1 in T2D vs controls	(19)
2	MWM	C57BL/6 mice	8 weeks	Unknown	Type 2 and diabetic encephalopathy model; HFD diet for 8 weeks and received streptozotocin at 30 mg/kg i.p.	Increased escape latency and decreased platform crossings during the space exploration phase; decreased	Hippocampal expression of CD86 increased and decreased expression of CD206 when co-labeled with IBA-1 in T2D group mice vs control;	(45)

						time in platform quadrant in T2D animals vs controls.	Decreased expression of Arg1, but expression of TNF and IL-6 increased in T2D.	
3	MWM, NORT	C57BL/6J mice	8–12 weeks (weighing 20–30g)	Male	HFD (460 kcal per 100 g, 45% fat). for 12 weeks. After 1 week of HFD, the mice were given streptozotocin (40 mg/kg, i.p.)	T2D increased escape latency and path length, while the swimming speed, the time spent in the target quadrant and the number of platform crossings were decreased compared to controls. T2D decreased time spent exploring the novel object compared to controls.	Based on scRNA-seq analysis of the db/db hippocampus, the number of microglial cells was increased vs controls. The enriched pathways were those related to: -protein synthesis machinery: ribosome, polysome, structural constituents of the ribosome -protein degradation systems: ubiquitin-protein ligase binding -proteolysis: peptidase and endopeptidase activity, apoptosis-related protein degradation -KEGG pathways: ribosome, apoptosis-related pathways, and viral infection–related pathways.	(17)
4	MWM, puzzle box	C57BL/6 mice	6 weeks	Male	diet-induced obesity (DIO) mice (380050) and C57BL/6 controls	Decreased latency to locate the platform at	Hippocampal microglia of HFD mice had fewer branch	(22)

					(380056) purchased from Jackson Laboratories DIO protocol for 6 months.	training day 2 in MWM after 1 month of HFD vs controls. Decreased executive functioning in puzzle box task, after 6 months on HFD	points in the hilus region versus control mice; Single-cell transcriptomics of distinct brain regions, including hippocampal region showed enriched neurodegenerative and inflammatory or immune response pathways.	
5	MWM, Y-maze	C57BL/6J mice	4 weeks	Female	HFD (D12492, 524 kcal/100 g, 60% energy as fat) impaired glucose tolerance vs controls	HFD animals showed decreased spatial learning during MWM training days and decreased latency to first entry in the platform zone in probe trial vs controls. In Y-maze, HFD animals showed fewer total arm entries, rotation, and alterations vs controls.	HFD-fed mice had more microglia with larger soma in the hippocampal CA1 and CA3 regions than controls.	(25)
6	MWM	C57BL/6 mice	6 weeks (weight 20 ± 3 g)	Male	Not precise; HFD and high-cholesterol diet (sunflower seeds and egg yolks added to standard chow). After 4 weeks of feeding, streptozotocin	Decreased spatial learning during MWM trainings and decreased time spent in platform quadrant and	IL-22-induced microglial transformation from homeostatic to reactive phenotype. Increased IL-22Rα1	(18)

					(100mg/kg i.p.) was applied.	number of platform zone crossings in probe trial was found in HFD animals vs controls.	(receptor) in Iba-1+ cells in diabetes model vs controls. Increased levels of IL-1β and TNF-α in the diabetes model animals vs controls.	
7	MWM, NORT, Y-maze	C57BL/6 mice	6 weeks	Male	Diabetes model (most likely type 2). After 8 weeks of HFD diet (60% of calories from fat, 5 kcal/g), the model mice were injected with streptozotocin (100 mg/kg, i.p.).	Decreased time spent and latency to entry in target quadrant in probe trial in HFD animals vs controls. Decreased novel object recognition and novel arm preference in diabetes model mice vs controls.	The number of IBA-1-positive cells and the ratio of activated microglia to the total number of microglia were increased in the hippocampus of diabetes model mice vs controls; increased prevalence of CD68+ microglia in diabetes model mice vs controls.	(20)
8	MWM	C57BL/6 mice	8 weeks	Male	After 4 weeks of the HFD, comprising 68% regular feed, 20% sucrose, 10% lard, 1.5% cholesterol, and 0.5% bile salts, single dose of streptozotocin (100 mg/kg, i.p.) was administered.	Decreased spatial learning during MWM training days and number of platform zone crossings in probe trial of HFD animals vs controls	In the hippocampus of model mice, the Iba1+iNOS+ positive area was increased, while Iba1+CD206+ positive area was decreased vs controls. Protein levels of TLR4, MyD88, and p-NF-κB/NF-κB in the hippocampus of diabetic mice were higher compared to the controls.	(35)
9	MWM, NORT	C57BL/6 J mice	8 weeks	Male	HFD mice were fed a 60% kcal fat diet (D12492), while normal control diet	Decreased spatial learning during	Increased colocalization of PSD95 with LAMP1 in the	(24)

					(NCD) mice were provided a 10% kcal fat diet (D12450B) from the age of 8 weeks to 33 weeks.	MWM training days and number of platform zone entries in probe trial of model animals vs controls. HFD mice showed reference index for the novel object at the control level after NORT 1h, while it was decreased after 24h.	Iba1+ cells in the BLA and CA1 regions, indicating that the reduction in synapses might be related to the enhanced synaptic uptake by the microglia in the HFD mice brains vs controls. Microglial activation in the BLA and CA1 regions in the HFD mice. Increased expression of polarization markers CD86, Arg1, and Mrc1 and proinflammatory factors TNF-α and IL-1β in the microglia of the HFD mice brains.	
10	Step-Through Passive Avoidance Test	C57BL/6N and KK-Ay/TaJcl	Animals were tested at 7- or 50-week-of age (aging effect)	Male	Diabetes type 2 mouse model in specific pathogen-free mice.	The step-through latency time as a measure of non-spatial long-term memory was decreased in 10- and 50-weeks old KK-Ay/TaJcl vs controls.	In the hippocampus, Iba1, CCR7, iNOS, TNF-α, and NO in KK-Ay/TaJcl Mice were increased, which was further exacerbated by aging. Neither CD163 nor arginase-1, the markers of M2 macrophages, were affected by model or aging.	(12)
11	MWM	C57BL/6J mice	4 weeks	Male	HFD for 12 weeks	Decreased spatial learning during	In hippocampal microglia in IR mice exhibited morphological	(33)

						MWM training days, as well as number of platform zone crossings and time in the target quadrant in probe trial in HFD animals vs controls.	activation characterized by increased Iba1 expression and amoeboid-like features with enlarged soma and retracted processes. Furthermore, increased mRNA levels of TNFα, IL-1β, CD86, IL-6 in model mice indicate that these activated microglia were polarized toward a pro-inflammatory M1 phenotype.	
12	Y-maze	C57BL/6J mice	4 weeks	Male	After 4 weeks of HFD, mice injected with streptozotocin (35 mg/kg, i.p.); HFD administered for 24 weeks in total.	The percentage of spontaneous alternations was decreased in T2D vs controls.	Increased number of Iba1+ cells in the cortex and CA1 hippocampus in T2D; in the T2D hippocampus increased levels of IL-1β, TNF-α and IL-6 were detected by western blot.	(4)
13	MWM	C57BL/6J mice	8 weeks	Male	Animals were fed by HFD diet (60% calories from fat) for 16 weeks and streptozotocin (100 mg/kg) was administered.	The T2D mice mainly swam on the edge of the pool and had a reduced platform crossing number compared to controls.	The immunofluorescence assay showed a stronger presence of Iba1-positive microglia in the hippocampus of T2D mice vs controls. The protein and mRNA levels of TNF-α, IL-1β, and IL-6 were upregulated in	(46)

							T2D mice vs controls. Microglia-mediated neuroinflammation by activating autophagy via TLR4/Akt/mTOR pathway.	
14	NORT	C57BL/6J WT and Mpak8 monotransgenic knockout animals (Jnk1−/−)	adults	Male	HFD induced hyperglycaemia	Decreased discrimination index in HFD animals vs controls, which was reversed in HFD fed KO Jnk1−/− mice	Analysis of the profiles of microglia revealed that cells were more reactive in the HFD WT when compared to the controls. Reactiveness was evaluated regarding the size, color intensity, number, and ramification rates of the detected cells. In the Jnk1−/− experimental groups, a reduction in these same characteristics was observed even below control levels.	(11)
15	MWM, NORT, Y-maze, object location test (OLT)	C57BL/6 mice	adults	Male	HFD diet (16 weeks) and streptozotocin (100 mg/kg, i.p) on the 4th week	Decreased time spent and distance traversed in the target quadrant in probe trial in T2D mice vs controls. Decreased time spent in novel arm (Y-maze), % investigation	In the cortex, CA1, CA3 and DG, increased number of $Iba1^{+}$ cells in T2D model compared to controls. Decreased protein expression of M2 marker CD206 in the cortex and hippocampus of	(23)

						time of moved object (OLT) and % time exploring novel object (NORT) in T2D mice vs controls.	T2D mice vs controls.	
16	NORT, Barnes Maze Test	db/db mice	6 weeks	Male	HFD (60 kcal% fat, 20 kcal% carbohydrates, and 20 kcal% protein; or High-Carbohydrate Diet (7 kcal% fat, 73 kcal% carbohydrates, and 20 kcal% protein) (HCD) for 12 weeks. Specific pathogen-free (SPF) db/db mice (BKS-Leprem2Cd479/Gpt) and WT mice.	HFD impaired novel object recognition in db/db and WT group, while HCD feeding reduced the frequency of exploring new objects in db/db mice; impaired spatial memory in Barnes maze in db/db mice after HFD or HCD diets.	In HCD fed db/db mice, increased abundance of Iba1+ microglia in the hippocampus vs controls was shown. In wild type mice, an HCD did not increase the quantity of IBA1+ microglia, whereas an HFD did. Gene expression of IL-1β, IL-6 and TNF-α were increased in WT and db/db mice fed by HFD, but HCD increased them only in db/db mice vs respective controls.	(21)
17	MWM and NORT, fear conditioning	db/db mice	7–8 weeks	Male	db/db mice (BKS.Cg-m+/+ Leprdb/J) and their age- and gender-matched normoglycemic heterozygous littermate db/m (BKS.Cg-m+/+ Leprdb/+/J) controls	Decreased spatial learning during MWM training days, as well as the percentage of distance and time spent in target quadrant during the	An Iba1 immunofluorescence assay demonstrated increased number of microglia in db/db mice vs controls in the hippocampus. Increased levels of IL-1β and IL-18 were identified in	(47)

						probe test in db/db mice vs controls. Decrease d discriminatio n index in NORT in db/db vs control mice. In the fear-conditioning test, db/db mice froze less than control mice in both the contextual and cued fear-conditioning trials.	db/db vs controls. Increased levels of RAGE, RIPK1 and p-RIPK1 in db/db mice vs controls.	
18	MWM, NORT	db/db mice	Animals were tested at 6, 18, and 26 weeks of age	Male	Diabetes type 2; db/db (BKS-Leprem2Cd479/Gpt) and age-matched WT (wild-type) (C57BLKS/JGpt)	Decreased spatial learning during MWM training days and number of platform zone crossings and time in the target quadrant in probe trial of HFD animals vs controls, but only at 18 weeks and 26 weeks of age. Short-term and long-term object recognition was impaired in db/db mice of 18 or 26 weeks of age vs their respective controls.	Increased microglial activation (Iba-1) in the hippocampus and cortex at 18 and 26 weeks of age was found in db/db mice vs controls. Increased brain levels of pro-inflammatory cytokines (IL-6 in 18 weeks old mice, TNF-α in 18 and 26 weeks old mice) were detected in db/db mice vs controls.	(26)

19	MWM, Actimetry and NORT	Control (APP/PS1–/– db/db+/+, APP/PS1–/– db/db± mice), db/db (APP/PS1–/– db/db–/– mice)	adults	31–34 females and 37–40 males randomly assigned to the groups (8 groups in total, some of them were treated)	db/db mice as model of diabetes	Decreased spatial learning during MWM training days in db/db mice vs controls.	Microglial burden 50 µm far from plaque was increased in db/db mice vs controls in the cortex, but not in the hippocampus.	(31)
20	MWM, NORT	db/db mice	adults	Female and males randomly assigned to the groups.	db/db mice vs controls	Decreased spatial learning during MWM training days in db/db mice vs controls, and decreased time during MWM probe retention test (48h) in target quadrant in db/db vs controls.	In SP-free areas, microglia burden was increased in db/db in the cortex, but not in the hippocampus.	(30)
21	MWM, Actimetry and NORT	db/db mice	6-month-old	Unknown	Wild type, db/db and db/+ mice	Episodic memory impaired in db/db mice vs controls in NORT. Spatial learning during MWM training days in db/db mice vs controls was impaired, as well in probe trials and retention trial.	Microglial burden was increased in the cortex of db/db mice (reduction in microglial size and density), as well as in the hippocampus, compared to controls.	(13)

22	MWM	KK-A^y mice	7 weeks (weighing 28–30 g)	Male	Diabetic model group; KK-A^y mice vs C57BL/6J mice as controls. KK feed	Decreased time in the target quadrant and number of platform zone crossings in probe trial of HFD animals vs controls.	Iba-1 expressions were higher in the hippocampal CA3 region of diabetes model mice compared to control mice. The hippocampal mRNA expressions of the proinflammatory cytokines TNFα, IL-1β, and IL-6 were increased in the diabetes model mice vs controls.	(14)
23	MWM	Sprague-Dawley ats	8 weeks	males	Diabetic cognitive impairment (DCI); homemade HFD and high-sugar diet, comprising basic feed (59 %), white granulated sugar (20 %), lard (18 %), and barnyard egg (3 %) for one month, after which they were injected with streptozotocin (35 mg/kg, i.p.).	Decreased spatial learning during MWM training days and number of platform zone crossings in probe trial of model animals vs controls.	The hippocampal DG region of the model group showed a significant enrichment of activated microglia vs controls; In the hippocampus, the expression of p-PI3k, p-Akt, and p-mTOR proteins was downregulated in the model group vs controls.	(28)
24	MWM, Delayed Alternation T-Maze Task (DAT)	Sprague-Dawley rats	Adults (~250 g)	Male	Rats were fed an HFD (20% carbohydrate, 20% protein, and 60% fat) for 2 weeks, followed by one injection of streptozotocin (30 mg/kg, i.p.)	T2D rats did not adopt the win-shift and lose-shift strategies in the DAT task, resulting in a reduced proportion of correct choices. In	The number of CD11b-stained microglia was higher in T2D rats than in controls and were amoeboid in shape. The expression of TNF-α and IL-1β in the hippocampus	(9)

						the MWM probe trial, T2D rats spent less time in the target quadrant, crossed the former platform location fewer times, and swam at a greater average distance from the platform than control rats.	was increased in T2D vs controls.	
25	NORT	Sprague-Dawley rats	9–12 month of age	Male	The HIP rat: a “humanized” animal model of hyperamylinemia as a model of T2D at 9–12 month of age; these Sprague-Dawley rats express human amylin in pancreatic β-cells	Diabetic HIP rats show a significant memory impairment, as indicated by reduced exploration of the novel object and decreased discriminatio n index as compared to controls.	Microglia/macro phages are particularly clustering around the small blood vessels in areas positive for amylin infiltration, as shown by serial staining with amylin and ED1 antibodies. The expression of both M1 and M2 phenotypic markers are increased in the cortex of HIP rats compared to controls. Supernatant of brain homogenates from HIP rats show increased pro-inflammatory cytokines TNF-α and IL-6, while the anti-inflammatory cytokine IL-10	(10)

							was down-regulated vs controls.	
26	NORT, T-maze	Wistar rats	8 weeks	Male	Animals were fed a HFD diet (5736 kcal/kg, Ssniff) for 12 weeks; HFD-induced hyperglycaemia	Impaired recognition of the novel object during the first 3min of NORT in HFD rats vs controls; Decreased number of entries to novel vs familiar arm after 90 and 120 min intertrial interval in T maze in HFD group vs controls.	Number of microglial cells increased in rat hypothalamus of HFD-fed rats vs controls. The microglia cells were less ramified and more amoeboid in HFD group than in controls. Increased gene expression level of TNF-α in the hypothalamus of HFD-fed rats in comparison with controls.	(15)
27	Pre-training and visual discrimination (VD) tests and Motivation task in touch screen chambers	Zucker Diabetic Fatty (ZDF) rats	Adolescent and Young adults VD tests were performed (~week 4 to 10 of age), while the motivational tests were performed during either adolescence or early adulthood.	Males and females	Zucker Diabetic Fatty (ZDF) obese and ZDF lean rats (glucose was between 4 and 7 mmol/ during testing). At 14–16 weeks of age, the sampling was conducted.	Adolescent ZDF obese rats outperformed ZDF lean rats on visual discrimination performance independently of sex. When the motivation was assessed, no difference was observed in these two phenotypes of ZDF.	No changes in the number and morphology of microglia cells were observed between young adult ZDF obese and lean rats of both sexes.	(16)

Cognitive function is impaired in animal models of diabetes type 2

Based on the evaluated studies, animal models of T2D consistently showed impairments in hippocampal-dependent spatial learning and/or memory, although the severity and onset of deficits varied with species/strain and induction protocol (9–12). Thus, the highest number of evaluated studies used the C57BL/6 mice (15 studies in Table I), whereas the application of the high-fat diet (HFD) protocol combined with the intraperitoneal (i.p.) administration of streptozotocin was the most frequent (11 studies in Table I). Furthermore, the diabetic genetic models were also exploited for studying cognitive and microglial changes (genetically modified, diabetic-obese mice with mutation in the leptin receptor gene ($Lepr^{db}$) (13): 6 studies in Table I, and KK-A^y mice obtained by backcrossing the natural obesity-related gene A^y into KK mice (14): one study in Table I). Three studies evaluated in Table I are identified that used Sprague-Dawley rats (10), while in one study T2D was modeled on Wistar rats (15). One study evaluated in Table I was performed on a Zucker Diabetic Fatty (ZDF) rat model (obese fa/fa), which is a genetically derived model of T2D, resulting from a spontaneous mutation in the leptin receptor gene (fa) (16). Regarding the protocols for disease modeling, a single dose of streptozotocin is usually administered within the HFD-related protocol and is ranging from 30 mg/kg (17) to 100 mg/kg (18), while some protocols included multiple streptozotocin applications (19), which may also affect the severity of hyperglycemia and, consequently, cognitive changes. Furthermore, in addition to the HFD, one study evaluated in Table I used a high-fat/high-sugar diet combined with low-dose streptozotocin (19).

The Morris water maze (MWM) was the most commonly used test to assess cognitive performance in mice or rats (20 studies in Table I) and demonstrated cognitive impairment (Table I). However, the results are not fully consistent; some models showed impairment only in spatial learning (19), others showed changes in spatial reference memory during the probe trial (20), and some showed impairment in both domains (21). Genetic T2D models such as db/db mice displayed mostly robust cognitive impairments, with poorer MWM acquisition curves, reduced platform zone crossings, and worse retention performance at adult ages compared with controls (13). Other spatial tasks, such as the Barnes maze (21) or puzzle box (22), confirmed reduced spatial memory and executive performance in diet-induced models of T2D, suggesting that networks involving the hippocampus and frontal cortex are particularly vulnerable to chronic metabolic stress.

When object recognition memory was tested (13 studies in Table I), most of the T2D animals showed impaired short-term recognition memory in novel object recognition (NORT) (11) or object location tasks (one study in Table I) (23). However, one study in Table I has shown a reduced percentage of novel object preference after 24h in NORT in the HFD group compared to controls, while it remained at the control level in 1h NORT (24).

Additional tasks such as the Y-maze and delayed alternation T-maze (DAT) revealed deficits in working memory and cognitive flexibility in T2D models, with reduced spontaneous alternation or inability to adopt win-shift/lose-shift strategies (25).

In KK-Ay/TaJcl mice, non-spatial long-term memory in a step-through passive avoidance paradigm deteriorated with both diabetes and aging, indicating that T2D amplifies age-related decline across multiple cognitive domains (12). Likewise, in db/db mice, episodic or object recognition memory after 24h was impaired in adulthood (e.g., 18–26 weeks), whereas younger diabetic animals showed milder or no deficits, suggesting that the duration of hyperglycemia and insulin resistance, as well as aging process, critically modulates recognition memory decline (26). Moreover, regarding the former, prediabetic rats had intermediate cognitive changes in this model. Indeed, spatial learning and memory in MWM impairments worsened with age in that model, reflecting the combined effect of diabetes and aging (26). The age-related effects on cognitive impairment in T2D were tackled only in 3 studies (Table I) of this mini-systematic review (10, 12, 26), but they warrant further investigation in future research.

Microglial dysfunction and phenotype alterations in diabetes type 2

The cognitive disfunction manifested in T2D models which is evaluated in this review has shown association with hippocampal- and cortex-dependent microglial dysfunction (Table I). Almost all studies that examined microglia reported increased microglial activation in T2D models, reflected in higher microglial number, more amoeboid and/or hypertrophic morphology, and reduced process complexity in hippocampal (22, 17) and cortical regions (4, 13). These studies suggested transition towards to reactive M1 microglia phenotype due to metabolic dysregulation, as microglia co-labeled with Iba1 and CD86 increased in number in the cortex and/or hippocampus with upregulated CD86 (19) and reduced CD206 (19, 23) and arginase 1 (Arg1) expression (19). Further, Wang et al. reported increased expression of iNOS, in the T2D group compared with controls, further supporting M1 polarization of microglia in T2D model (19). In KK-Ay/TaJcl mice, aging and diabetes duration enhanced pro-inflammatory microglial markers (e.g., Iba1, CCR7, iNOS, TNF-α) without a corresponding upregulation of M2 markers such as CD163 or Arg1, suggesting limited capacity to mount an M2 response in this context (12). Partially in contrast, one T2D model based on hyperamylinemia in aging rats showed increased expression of M1 and M2 markers in the cortex compared to controls, followed by a decrease in IL-10 levels (10). These inconsistencies imply to complexity of the neuroinflammatory changes dependent on the model and age, but highlight the presence of the hyperreactivity of microglia except in one study selected in Table I (16), which could be associated with the T2D effect evaluation in young adult ZDF rats.

Of specific interest in relation to episodic and spatial memory in the T2D model is the reactivity and/or increase in the number of microglia in parts of the hippocampus (27), such as the CA1 or CA3 regions (23, 25). Furthermore, the T2D rat model showed significant enrichment of activated microglia in the dentate gyrus, associated with

downregulation of p-PI3K, p-Akt, and p-mTOR signaling in the hippocampus (28), linking the microglial dysfunction with impaired metabolism and survival system. Basolateral amygdala (BLA) is responsible for emotional regulation and influence the memory formation in the hippocampus (29). In HFD-fed C57BL/6J mice, microglia in the CA1 hippocampus and BLA were activated, showing increased Iba1 staining, enlarged cell body, and retracted processes, together with elevated expression of polarization markers CD86, Arg1, and manose receptor (Mrc1/206) and pro-inflammatory factors TNF-α and IL-1β in microglia (Ni *et al.*, 2024), suggesting the microglia-dependent disruption in BLA-hippocampus integration.

Several studies observed that microglial activation was particularly prominent around microvascular changes especially when the db/db model was combined with APP/PS1 background, suggesting a link between T2D-related neurovascular pathology and microglial responses (30, 31). Interestingly, in db/db mice, microglial burden increased in the cortex, but not in the hippocampus, with a higher number of microglia at some distance from plaques, while the immediate periplaque zone did not show a proportional microglial increase. This was especially shown in db/db mice crossed with the APP/PS1 background, suggesting that T2D may contribute to modifications in microglial spatial organization around pathological deposits in AD (31).

At the molecular level, microglial activation in T2D was accompanied by increased expression of pro-inflammatory cytokines, especially TNF-α, IL-6, and IL-1β (Table I).

Microglial changes in the context of cognitive impairment

Overall, studies that measured both behavior and microglial status support a strong association between microglial activation and T2D-related cognitive deficits (Table I). Microglia in the hippocampus showed activity in cognitive processes, with repopulation of microglia leading to improved cognition, while the microglial ablation did not have effect (32). However, this systematic review suggests that the changes in phenotype in addition to number can negatively affect the cognition. T2D models with cognitive impairments found in MWM and/or NORT almost invariably showed increased Iba1-positive microglial density, amoeboid morphology, and elevated TNF-α, IL-6, and/or IL-1β levels in the hippocampus and cortex (Table I). In db/db mice, worsening of spatial learning and recognition memory across age was paralleled by increasing microglial burden and cytokine expression, indicating that chronic metabolic stress gradually drives neuroinflammation that tracks cognitive decline (12).

Several mechanistic observations suggest that microglia may directly contribute to synaptic dysfunction in T2D. In HFD-fed C57BL/6J mice, increased colocalization of the postsynaptic marker PSD95 with the lysosomal marker LAMP1 within Iba1-positive microglia in CA1 and BLA indicated enhanced synaptic engulfment, which likely underlies the reduction in synapse number and the observed memory deficits (24). In other T2D models, microglial M1 polarization was associated with the downregulation of neuronal PI3K/Akt/mTOR signaling and increased markers of apoptosis and gliosis,

further supporting a causal role of microglia-mediated inflammation in disrupting neuronal plasticity and survival (28).

Interventions that reduce microglial activation or promote a more protective phenotype often improved performance in MWM, Y-maze, DAT, and NORT tests in T2D animals. Fingolimod promoted M2 polarization through the pSTAT3–JMJD3 axis, with increased CD206 and reduced M1 markers, and alleviated cognitive deficits in a T2D model (23). Melatonin attenuated microglial activation, decreased TNF-α, IL-6 and IL-1β, and ameliorated T2D-associated cognitive impairments, although the balance between M1 and M2 markers varied by brain region (33). Pharmacological modulation of necroptosis (necrostatin-1s), S1PR2 inhibition, and TREM2/NF-κB signaling, as well as resistance exercise and caffeine, similarly reduced pro-inflammatory microglial markers and were associated with better cognitive outcomes in different T2D models (5, 6, 21, 33–35).

These studies jointly suggest that targeting microglial phenotype is a promising strategy to rescue T2D-related cognitive dysfunction, but they also emphasize the need to test whether such interventions differentially affect young versus aged animals and male versus female subjects. Regarding the latter, microglia may be sensitive on sex-dependent effects (36), but only one study selected in Table I assessed the sex-dependent effects and did not find any T2D-induced changes in microglia (16). Furthermore, one study from Table I was conducted only on female animals (25), while two studies randomly assigned females and males to the groups (30, 31), so further investigation in both male and female sexes in this context are needed to assess potential sex-related effects. In addition, most work relies on histology and bulk cytokine measurements; microglial heterogeneity at the single-cell level in T2D and its relationship to specific cognitive domains (spatial versus recognition memory) remains largely unexplored and represents an important future direction (17).

Pathophysiological links between diabetes type 2 and early-stage neurodegeneration

An increasing body of experimental and clinical evidence indicates that T2D leads not only to cognitive decline, but also initiates early neurodegenerative processes, including synaptic loss, neuronal dysfunction, and accumulation of pathological proteins in vulnerable brain regions (37, 38). Putative mechanisms by which T2D and its vascular and metabolic complications promote early neurodegenerative changes include mitochondrial dysfunction, oxidative stress, dysregulated brain cholesterol metabolism, low-grade inflammation, and cerebral microvascular injury (39, 40). In T2D, chronically activated microglial cells shift toward a pro-inflammatory and metabolically dysregulated state that contributes to early brain neurodegenerative changes (41).

In the animal models of T2D included in this review (Table I), in addition to cognitive impairment, mechanisms underlying early neurodegenerative changes were also identified. Expression of microtubule-associated protein 2 (Map-2) and neuronal nuclei (NeuN) in C57BL/6 mice exposed to a combination of HFD and i.p. streptozotocin

was significantly reduced in the hippocampus, indicating neuronal damage. Moreover, expression levels of Aβ and p-Tau were elevated in the hippocampus and prefrontal cortex of treated mice compared with controls. This was accompanied by a higher number of activated microglial cells in the hippocampus of treated mice (20). In AD-T2D mice, glucagon-like peptide-1 agonist liraglutide attenuated neuronal loss and brain atrophy (31). Also, the sodium-glucose cotransporter 2 inhibitor empagliflozin reduced cortical thinning and neuronal loss in AD-T2D mice. Interestingly, neuronal loss was not observed in APP/PS1 mice, but was detected in APP/PS1xdb/db mice, thus more closely recapitulating AD pathology (30). It has been shown that HFD induces transcriptomic changes involving not only metabolic and inflammatory pathways, but also neurodegeneration-related pathways. Expression of AD- and inflammatory-related genes was selectively upregulated in microglia from HFD-fed mice (22). Furthermore, in rats overexpressing human amylin in the pancreas, an amyloidogenic hormone co-secreted with insulin, accumulation of oligomeric amylin was observed in the brain. These deposits induce molecular alterations in the brain structure, and activated microglia/macrophages were found to cluster around small vessels within amylin-positive regions (10).

The role of microglia in neurodegeneration becomes progressively more detrimental with aging. Age-related weakening of neuron-microglia regulatory axes, such as the CX3CL1-CX3CR1 signaling pathway, further disrupts homeostatic control, predisposing microglia to sustained activation (42, 43). In this context, aged microglia act as key amplifiers of neurodegenerative cascades in disorders such as AD and Parkinson's disease, especially if hyperglycemia exists (44).

Conclusion

Animal models of T2D consistently show that chronic metabolic stress impairs multiple cognitive domains and is closely linked to microglial dysfunction, particularly within hippocampal and cortical circuits. These models also reveal early neurodegenerative changes, including neuronal loss, synaptic alterations, and Alzheimer's disease-like pathology. Collectively, these findings position microglia at the intersection of metabolic dysregulation and early-stage neurodegeneration in T2D, and highlight microglial signaling pathways, metabolic reprogramming, and inflammatory mediators as promising therapeutic targets whose modulation may prevent or attenuate diabetes-associated neurodegeneration.

Acknowledgement

This research was supported by the Science Fund of the Republic of Serbia, 10203, Translational road to elucidate the effects of GLP-1 receptor agonist treatment on adipose tissue-brain axis function in cognitive processes in diabetes type 2 with concomitant obesity – COD-GOAT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This study received no financial support.

Author contributions

J.A.: Conceptualization, Writing – original draft, review & editing; **J.Đ.**: Conceptualization, Writing – original draft, review & editing.

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Mikroglijalna disfunkcija i kognitivno oštećenje u animalnim modelima dijabetesa tipa 2: sistematski pregled koji povezuje dijabetes i ranu neurodegeneraciju

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Kratak sadržaj

Dijabetes tipa 2 (T2D) usko je povezan sa kognitivnim oštećenjem i povećanim rizikom od demencije. Smatra se da rane neuropatološke promene u T2D obuhvataju neuroinflamatorne procese, što ukazuje da funkcija mikroglije u dijabetičnom mozgu može biti narušena ili pomerena ka maladaptivno aktiviranom stanju. Rastući broj dokaza implicira disfunkciju mikroglije kao ključni mehanizam u osnovi kognitivnog oštećenja povezanog sa T2D. Promene u prostornom učenju, memoriji i izvršnim funkcijama prate funkcionalne i fenotipske alteracije mikroglijalnih ćelija, naročito unutar hipokampalnih i kortikalnih moždanih krugova. Istovremeno se javljaju rane neurodegenerativne promene, uključujući gubitak neurona, sinaptičke alteracije, akumulaciju Aβ i p-Tau, kao i transkriptomski potpis karakterističan za Alchajmerovu bolest (AD) u vulnerabilnim moždanim regionima. Starenjem mikroglija sve značajnije doprinosi neurodegeneraciji, jer njene regulatorne interakcije sa neuronima slabe, što pogoduje njenoj trajnoj aktivaciji. Ovaj mini sistematski pregled ima za cilj da sintetizuje aktuelne *in vivo* nalaze o odnosu između kognitivnog oštećenja i promena mikroglije u animalnim modelima T2D i da razgraniči osnovne patofiziološke mehanizme koji povezuju hronični metabolički stres, disfunkciju mikroglije i rane neurodegenerativne promene. Dodatno, nastoji da istakne kako ovi mehanistički putevi, koji obuhvataju signalizaciju mikroglije, inflamatorne medijatore i metaboličko reprogramiranje, mogu predstavljati obećavajuće terapijske targete za prevenciju ili ublažavanje neurodegeneracije povezane sa dijabetesom.

Ključne reči: dijabetes tipa 2, animalni modeli, kognitivno oštećenje, mikroglija, neurodegeneracija