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Review

The changes in cognitive function following bariatric surgery considering the function of gut microbiome

Milad Kheirvari [a], Vivienne A. Lacy [b], Hamidreza Goudarzi [c], Nima RabieNezhad Ganji [d], Mona Kamali Ardekani [e], Taha Anbara [e,*]

[a] Microbiology Research Centre, Pasteur Institute of Iran, Tehran, Iran
[b] Department of Biology, Texas Tech University, Lubbock TX, USA
[c] Department of Surgery, Erfan Niayesh Hospital, Tehran, Iran
[d] Department of Experimental Oncology and Surgery, University of Palermo, Palermo, Italy
[e] Medical Research Center, Tandis Hospital, Tehran, Iran

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ABSTRACT

Background: There is a correlation between gut microbiota and cognitive function. The mechanisms and pathways explain why the incidence of Alzheimer's disease in subjects undergoing bariatric surgery is lower than in other people with obesity.
Methods: In this review article, we aim to discuss the association of obesity, cognitive impairment, and physiological changes after bariatric surgery.
Results: Bariatric surgery has a series of physiological benefits which may lead to an improvement in cognitive functions in individuals who are prone to later developing Alzheimer's disease. Also, taxonomical change in the gut microbiome profile provides a healthy condition for living with better levels of cognition without neuropathological damages in older ages.
Conclusion: It can be concluded that there is a possible correlation between cognitive dysfunction and increased risk of cognitive dysfunction in people with a BMI higher than 40 kg/m^2. Bariatric surgery may increase neurotransmitters and improve the gut bacteria, leading to a significant reduction in the risk of Alzheimer's disease.

1. Introduction

Obesity is an unresolved and undeniable issue in developed countries, with its prevalence tripling over the past 40 years [1]. Reliable treatments for people with a BMI higher than 40 include surgical methods such as Roux-en-Y gastric bypass (RYGB), adjustable gastric band (AGB), and laparoscopic sleeve gastrectomy (LSG) [2]. Based on previous reports, patients experience 15 to 20% loss in total weight after surgery using these methods [3]. While neural responses to food and food cues can predispose subjects to uncontrolled eating habits, these processes are also controlled by some cognitive agents. Deficits in attentional bias, delay discounting, and episodic memory have clear connections to overeating in bench and bedside settings. The weight loss interventions affect the mentioned deficits through strategies designed to either directly improve cognitive function or circumvent them by tailoring weight management strategies to patients' specific cognitive profiles [4]. Bariatric surgery (BS), as a weight loss intervention, has a series of benefits for patients that results in improving quality of life, weight loss, and metabolic pathways. The most important modifications are the reductions in glucagon secretion and glucose production in the liver, hunger, β-cells apoptosis and glucagon secretion in the pancreas; and an increase in glucose uptake and storage in muscles, β-cells proliferation, pancreatic hormone secretion, insulin secretion/biosynthesis and bile secretion in the gallbladder [5]. In an innovative study, results suggested that cognitive impairment is an independent contributor to poorer total and work-related quality of life in candidates undergoing bariatric surgery [6]. Mild cognitive impairment is a predictive factor for Alzheimer's disease (AD) and cognitive dysfunction. These factors were found to be more common in individuals with obesity [7,8] and in patients undergoing BS due to their elevated BMI, with one report showing more than 50% of patients undergoing BS being diagnosed

* Corresponding author, Department of Surgery, Erfan Niayesh Hospital, PC 1476919491, No. 17, Bahar Intersection, Imam Hossein St., after Kabiri Tameh Blvd., Niayesh Gharb Highway, Tehran, Iran.
E-mail addresses: Milad.kheirvari@ttu.edu (M. Kheirvari), vivienne.lacy@ttu.edu (V.A. Lacy), Hamidreza24@live.com (H. Goudarzi), Nima.rabienezhadganji@unipa.it (N. RabieNezhad Ganji), Kamal.m40@gmail.com (M. Kamali Ardekani), drtahaanbara@dranbara.com (T. Anbara).

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with mild cognitive impairment [9,10]. Underlying mechanisms including a rise in tau protein and neurofibrillary tangles, the build-up of amyloid plaques and neuroinflammatory processes, brain atrophy, as well as premature synaptotoxicity may put elderly people in danger of AD [9]. To shed light on the sequelae of obesity on cognitive function, researchers evaluated key factors and found that the distribution of white adipose tissue (WAT) plays an important role [7,10]. Specifically, the abdominal WAT leads to an increase in inflammation and AD-related adipokines such as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), interleukin-β (IL- β), and IL-6 [11]. Beside the effects of IL-6 on hippocampal volume/function, the inflammation and enhanced cytokine levels may cause 1) cardiovascular diseases such as hypertension thrombosis, atherosclerosis, and endothelial dysfunction, 2) poor blood circulation leading to a reduction in Cerebral Blood Flow (CBF) resulting in decreased cognitive function [12], 3) damages to food-intake regulating circuits of the brain [13] and 4) affects other adipokines expression i.e. angiotensinogen, serum amyloid A (SAA), and plasminogen activator inhibitor-1 (PAI-1) [5]. In terms of brain structure and function, higher levels of leptin released by fat cells are closely related to a reduction in grey matter (GM) volume in people with obesity (Fig. 1) [10]. These elevated levels of leptin also affect the energy intake regulation in hypothalamus neurogenesis, memory, and brain structure [14,15]. When it comes to food-related stimulus processing, cases with obesity illustrate 1) a reduction in volume of the frontal operculum, post-central gyrus, dorsal striatum, hippocampus, and prefrontal cortex; 2) an increased activation in some regions of the brain including the nucleus accumbens and caudate nucleus when a sweet, bitter, and high calorie diet is consumed; and 3) a decreased connectivity in reward-related networks (Fig. 1) [16]. Surprisingly, this food-related stimulus processing demonstrates that these alterations lead to obesity rather than obesity leading to this food-related processing in the brain [17]. When it comes to cognitive function and obesity control, a reduction in memory performance and learning abilities due to a significant decrease in brain activity in some regions associated with learning, as well as an inadequate implicit learning caused by lower dopamine signaling can be seen in people with higher BMI [18]. Additionally, higher impulsivity and lack of inhibitory control are other reasons for decreased accuracy resulting in lower cognitive function [10]. With current findings, researchers believe that the gut, its hormones, and microbiome may have undeniable impacts on brain structure and cognitive function. For instance, short-chain fatty acids (SCFAs) produced by intestinal microbes play a major role in the production of neurotransmitters and their precursors [19]. Nota et al., claimed that the WAT and the gut microbiome would be the cornerstones of any changes in brain function [10]. Based on multiple studies, the gut microbiome may have both positive and negative effects on the brain and therefore may facilitate or impede the progress of AD [20,21]. Moreover, an altered microbiome enhances the production of β-amyloid, a hallmark of AD [22], therefore diet may affect the progression of AD through altered gut bacteria. As mentioned previously, BS is completely associated with the changed dietary pattern, eubiosis/dysbiosis of microbiota, and physiological revolution after the procedure [20,23], hence it seems meaningful that this type of surgery may have a considerable impact on the progression of AD. In this study, we aim to describe the influences of the gut microbiome on the pathogenesis of AD following BS in subjects with obesity by evaluating existing research findings and identifying gaps in the knowledge required to advance our understanding of the pathways (see Table 1).

2. The impacts of obesity on Alzheimer's disease

A study with 18 years of follow-up reported a 36% increase in the risk of AD, with each one unit increase in BMI in elderly women [24]. Therefore, AD progression is raised in individuals with obesity through a

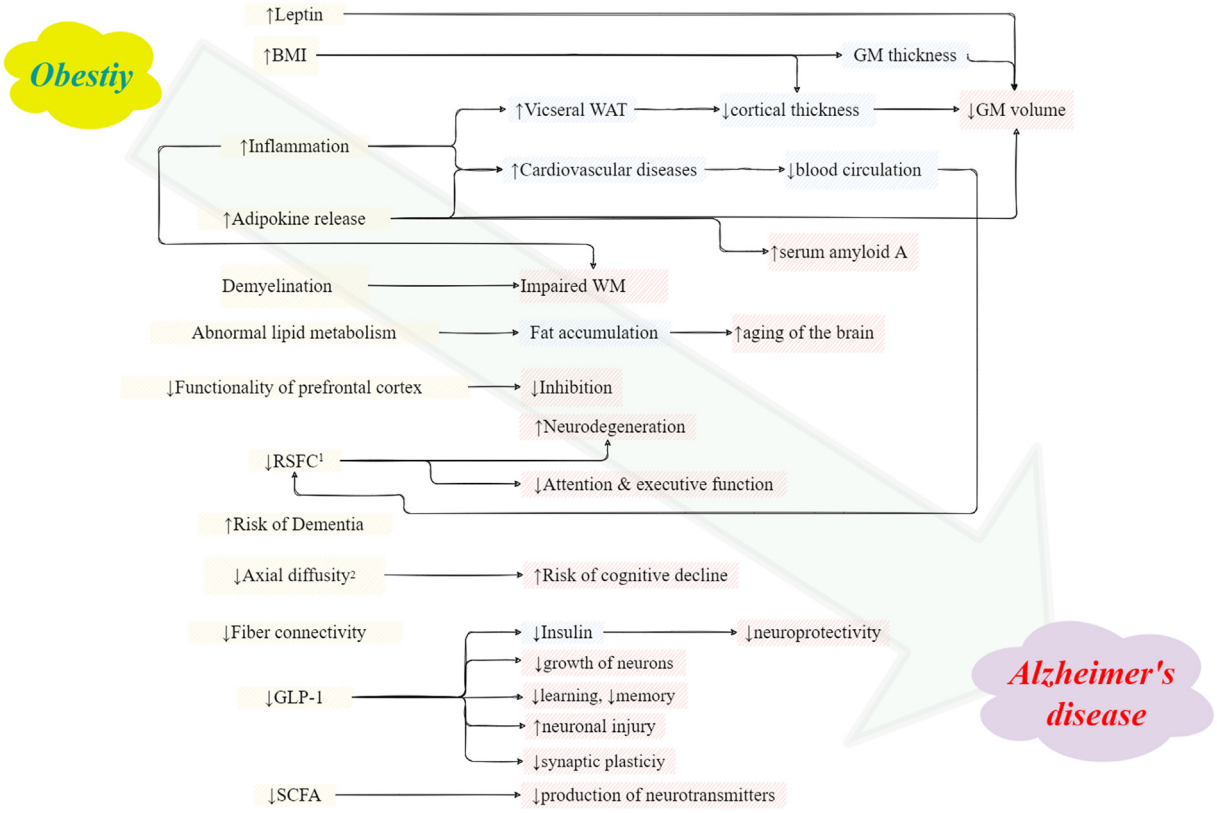

Fig. 1. Sequelae of obesity resulting in decline in cognitive function, brain structure and increased risk of Alzheimer's disease. Adipokines such as monocyte chemoattractant proteins-1 (MCP-1), tumor necrosis factor (TNF-α), Interleukin 6 and IL-β, angiotensinogen, and plasminogen activator inhibitor-1 (PAI-1). Abbreviations: WAT, white adipose tissue; GM, grey matter; WM, white matter; RSFC, resting-state functional connectivity. Notes: 1) Reduction in RSFC in middle frontal gyrus; 2) Decrease in axial diffusivity in corticospinal tract, anterior thalamic radiation, and superior longitudinal fasciculus; 3) Insulin act as growth factor for brain.

Table 1
Taxonomic profile of the gut microbiome in AD patients after bariatric surgery.

Taxa	Reported change in AD	Reported change after LSG	Reported change after RYGB
Firmicutes			
Firmicutes	↑ [51]	↓ [50]	↑ [52]
Faecalibacterium	↓ [51]	↑ [55]	↓ [53]
F. Prausnitzii		↓ [58]	↓ [53]
Clostridiales	↑ [51]	↑ [59,60]	N/A
Steptococcus	↑ [51]	N/A	↑ [53]
Blautia	↑ [51]	↓ [50], ↑ [52]	No change
Veillonella	↓ [51]	Partially ↑ [52]	↑ [53]
Clostridium	↓ [51]	↓ [55]	↑ [52]
Roseburia		N/A	N/A
Eubacterium	↓ [51]	↑ [52]	Partially ↑ [52]
Dorea spp.		↓ [55]	↓ [61]
Listeria		N/A	N/A
Ruminococcaceae	↑ [51]	↑ [59]	N/A
Bacteroidetes			
B. fragilis		↑ [62]	↓ [61,63]
Alistipes spp.	↑ [51]	↑ [50]	↑ [53]
Verrucomicrobia			
Akkermansia	↓ [51]	↑ [52]	↑ [53]
Actinobacteria			
Bifidobacterium	↓ [51]	↓ [52]	↓ [63] ↑ [53]
Actinobacteria	↑ [51]	↑ [50]	N/A
Collinsella		↓ [52]	↓ [52]
Proteobacteria			
Helicobacter		↓ [50]	N/A
E. coli	↓ [51]	↓ [54]	↑ [53]
Enterococcus		↑ [50]	↑ [53]
Fusobacteria			
Fusobacterium spp.		↓ [52]	↑ [53], ↓ [52]
F. nucleatum		N/A	↑ [50,53]
Bacteroidetes			
Bacteroides	↓ [51]	↑ [52]	↑ [52]

series of changes in metabolic and physiological pathways, distinct from people with normal weight or individuals with lower BMI [7]. Obesity-related systemic inflammation promotes insulin resistance in several organs specially brain, resulting in hyperinsulinemia and hyperglycemia which subsequently contribute to Aβ accumulation and lack of degradation of misfolded and hyper-phosphorylated tau protein [25]. On the other hand, enhanced inflammatory cytokines may gain access to the brain through blood brain barrier, leading to reduced synaptic plasticity and impaired neurogenesis [26]. In addition, a reduction in regional CBF in the prefrontal brain regions is an obvious part of these changes in people with obesity which can lead to neurodegeneration and lower attention, reasoning, and executive function. Also, people with higher BMI illustrate increased aging of the brain, increased risk of dementia, and activity of synchronicity [27]; as well as decreased critical thickness (as measurement factor for GM), GM volume, white matter (WM) volume (impaired WM microstructure due to demyelination), fiber connectivity, axial diffusivity, resting-state functional connectivity (RSFC), functionality of (pre)frontal cortex and eventually inhibition [8,10,16]. As far as the effect of BMI on WM integrity is concern, studies reported that fibre integrity was reduced with increased BMI in the entire corpus callosum, the largest WM structure in the brain. Decreased fibre integrity was observed pointing to demyelination in the fornix with increasing BMI. However, based on a report, this effect is diminished after correcting for vascular and inflammatory markers.

In general, these results demonstrate that obesity is mainly related to axonal damage accompanied with demyelination in WM [28]. Fig. 1 demonstrates the impacts of obesity on cognitive function, brain structure, and risk of AD in more detail.

3. The effects of bariatric surgery on Alzheimer's disease

More than half a sample of pre-surgical patients undergoing bariatric surgery met the criteria for mild cognitive impairment [7]. In this study, participants completed the computerized cognitive battery exams and questionnaires within 30 days before surgery and 12 months post-operatively. It has been reported that shortly after BS, subjects demonstrated an obvious improvement in cognitive control, change in brain activation, increase in predominantly memory domains, and increased executive function [8,29,30]. One month after LSG, individuals illustrated an increase in WM integrity and connectivity [10]. At the 12-week follow-up period, attention/executive function and memory abilities were increased and cognitive impairment became less prevalent in post-bariatric subjects than pre-bariatric individuals [31]. Six months after BS, an obvious improvement in GM and WM density can be seen in almost all bariatric cases [8,31,32]. Reports by Alosco et al., illustrated that 24 months after the surgery, improved memory, decreased inflammation and lower expression of AD-related proteins (i.e. amyloid precursor protein (APP)) were found among patients with obesity [32]. Although some researchers believe that the most common postoperative complication of BS, nutritional deficiencies, may put patients in danger of cognitive dysfunction [33]; the mechanisms and pathways show that BS might be a part of the process in reversion cognitive impairment associated with obesity [29,34,35]. Not only does the weight loss following BS immediately result in improved cognitive function, but also the neuroprotective effects of BS can be seen up to 3 years after the procedure [10]. One of the most crucial changes in patients undergoing bariatric surgery is in Glucagon-like peptide-1 (GLP-1) levels, which is responsible for a series of metabolic pathways after surgery [36,37]. GLP-1 levels demonstrated a 5–10 fold increase after the procedure, leading to higher secretion of insulin – a neuroprotective hormone that also acts as a growth factor for the brain [38,39]. GLP-1 benefits the central nervous system (CNS) with neuroprotective and neurotrophic effects, thereby helping increase memory and learning abilities [40,41], while also increasing synaptic plasticity, the growth of neurons, and reducing neuronal injury after BS [9]. Understanding the relationship between obesity and cognitive function is crucial for the identification of potential therapeutic and prophylactic targets. Some researchers are testing several diabetes therapies that enhance insulin signaling for a potential therapeutic benefit in dementia. Furthermore, disruption of insulin signaling, however, makes neurons more vulnerable to metabolic stress, thus accelerating neuronal dysfunction. Defective insulin signaling is associated with decreased cognitive ability and the development of dementia [42]. Interestingly, BS through GLP-1 can reduce the risk of AD even in diabetic non-obese patients [43]. Patients undergoing bariatric surgery illustrated a reduction in blood oxygenation level-dependent (BOLD) signal, important for the rewarding process; changes in RSFC, affecting self-referential processing, learning and eating behavior; alteration in adipokine secretion leading to increased CBF; improvement in the gut pattern and its hormones [44]; reduction in APP and its mRNA; expression of activator protein-1 (AP-1) (β-amyloid activates AP-1 leading to inflammation); other pro-inflammatory mediators (i.e. CRP and MCP-1); and AD-related genes even 3–4 years following RYGB or LSG [10]. Fig. 2 shows schematic information on the possible changes in biological pathways following BS resulting in a reduction in risk of AD in patients.

4. The effects of bariatric surgery on Alzheimer's disease through microbiome

Physical activity and the gut microbiome independently influence cognitive function. Regular and supervised exercise mediates the composition of the gut microbiome, while cognitive improvement due to physical activity may be partially controlled by the gut microbiome [45]. The gut microbiota plays a key role in metabolic pathways, especially following BS, leading to improvement in both obesity-related complications and non-obesity-related disorders [46]. Based on previous studies, impairment in the microbiome can lead to cerebrovascular degeneration and inflammation [2,19], while reduction in cytokines levels (such as IL-6, MCP-1,

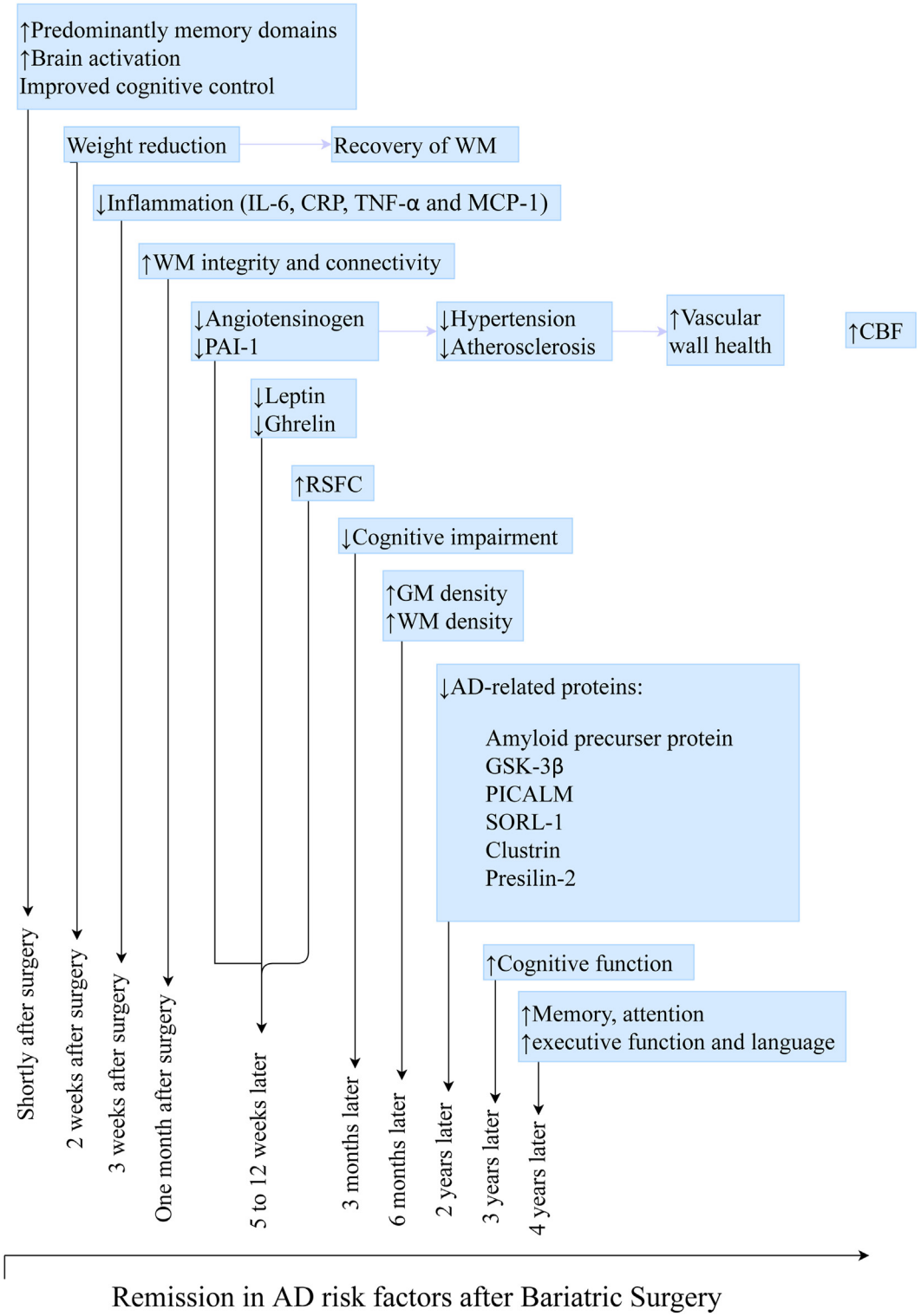

Fig. 2. Changes in physiological and neurological parameters leading to remission in AD risk factors after Bariatric surgery.

and TNF-α) and inflammation after BS result in lower metabolic stress, subsequently leading to an increased hippocampal GM volume and memory improvement. Changes in gut hormone secretions such as fasting ghrelin levels (caused by increased GLP-1 and postprandial peptide YY) lead to the regulation of energy homeostasis in the brain and functional brain changes (Fig. 3). Given the fact that reduction in ghrelin levels results in increased connectivity in regions for self-control and executive functions, an improvement in hippocampus and brain reactivity can be observed. Based on a study by Zhang et al., in 2020, the gut microbiome, influenced by neuroprotective dietary patterns, illustrated positive impacts on the brain including an increase in nerve membrane as well as a reduction in Dendritic lesions, neuron apoptosis, accumulation of Aβ, tau disorder, inflammation and oxidation, and the risk of chronic disease [23]. Alternatively, the introduction of gut microbes to neuroimpaired dietary patterns revealed negative effects on the brain as well as AD progression facilitated by increased blood vessel injury, Aβ accumulation, tau

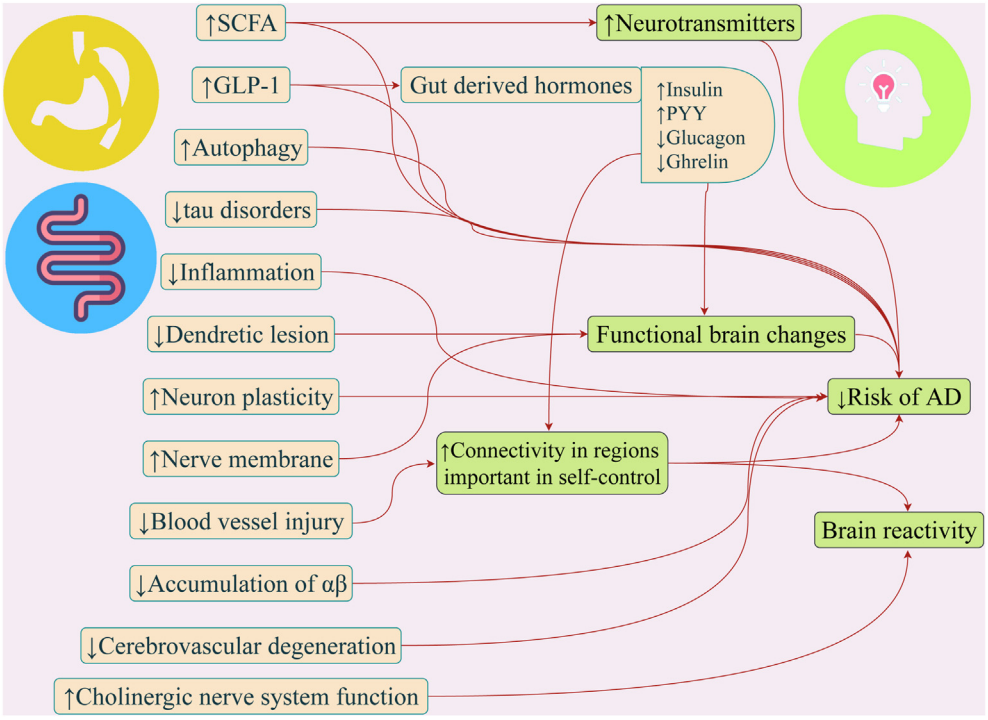

Fig. 3. Improvement in cognitive function as a result of Alzheimer's disease Eubiosis in the gut microbiota influences bariatric surgery.

phosphorylation, inflammation and oxidation, as well as lower neuron plasticity, autophagy, cholinergic nerve system function and finally decreased cognitive function in individuals [22]. As mentioned previously, patients undergoing bariatric surgery demonstrated a reduced occurrence of *Akkermensia mucinipila,* which is positively connected to hippocampal atrophy [23]. Researchers believe that dysbiosis features of the gut microbiome might be a potential indicator of early AD [47,48]. On the other side, eubiosis in this pattern concluded a reduction in the risk of AD in individuals following BS [19,23]. For instance, not only is inflammation-related *Erysipelotrichaceae* significantly associated with an increased risk of AD [23] and neuroinflammation (mostly caused by gut bacteria), it is also one of the pathological syndromes of AD [48]. In another study using animal subjects, the group which was fed milk containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* displayed a promoted cognitive function [49]. Moreover, altering the microbiome by decreasing *Streptococcus* spp., *B. subtilis*, *E. coli*, *Klebsiella pneumonia*, *Mycobacterium* spp., *Salmonella* spp., and *Staphylococcus aureus* enhanced the production of β-amyloid which is an important parameter for diagnosing AD [22]. An increase in *Firmicutes* and *Blautia* species has been reported, while a reduction in the mentioned bacteria has been reported in patients who underwent LSG cases but not in RYGB patients [50]. Also, changes in taxonomic profile in the gut bacteria of LSG and RYGB subjects are in the opposite side of reported dysbiosis in AD patients [51] such as a reduction in *Akkermansia* [52,53], *E. coli* [53, 54], *Faecalibacterium* (just in LSG cases) [55], *Veillonella* [52,53], *Clostridium* (Just in RYGB subjects) [52], *Eubacterium* [52], *Bifidobacterium* (just in RYGB subjects) [53], and *Bacteroides* [52]. Unfortunately, there is not enough evidence or reports for dysbiosis/eubiosis of gut microbiota after BS in relation to the status of AD and cognitive function. Changes in the gut bacteria after BS results in an increase of gut-derived hormones including insulin, GLP-1, peptide YY, glucagon, and ghrelin. These hormones lead to an increased connectivity in regions important for self-control including/as well as the hippocampus, consequently increasing brain reactivity and causing a series of functional changes in the brain [9]. Although some experts believe that nutritional deficiencies after BS may lead to memory impairment [56], changes in the gut microbiome (including an increase butyrate levels) play a crucial role in the reduction of memory impairment and the improvement of cognitive problems in patients [23]. An increase in BDNF is yet another physiological change caused by the gut microbiota providing neural growth in patients after bariatric surgery [57]. Accumulatively, eubiosis in the gut microbiome pattern leads to a physiological and metabolic revolution in patients by decreasing in inflammation, cerebrovascular degeneration, accumulating of αβ, tau disorders, nerve membrane, blood vessel injury, and dendritic lesion as well as increasing neuron plasticity, autophagy and cholinergic nerve system which results in a reduction in the risk of AD [9,23]. Alternatively, higher SCFA levels, one of the changes after BS [5], increases neurotransmitters and leads to a significant reduction in the risk of AD following BS [10]. The physiological and metabolic changes following BS are undeniable, but each type of BS such as LSG, RYGB, AGB has different impacts on patients with obesity. Therefore, researchers should determine the exact type of surgery for their target group of study.

5. Conclusion

It can be concluded that there is a possible correlation between cognitive dysfunction and increased risk of AD in people with a BMI higher than 40 kg/m^2. BS, on the other side, is a surgical treatment for weight loss having a series of physiological benefits which may lead to an improvement in cognitive functions in individuals who are prone to later developing AD. Another change following BS is a taxonomical change in the gut microbiome profile, providing a healthy condition for living with better levels of cognition without neuropathological damages in older ages. In addition, more specific studies needed to draw reliable taxonomical profiles of the gut microbiome in patients undergoing bariatric surgery divided by the type of surgery. On the other hand, rather than the type of surgery, there are also some other factors involved in the gut microbiome eubiosis/dysbiosis after bariatric surgery such as genetic background, nutritional habits and preferences after surgery, sedimentary or active lifestyle, the ability of body to overcome mentally with low intake meals and manage the levels of proteins/carbohydrates, which researchers may consider them as exclusion or inclusion criteria in their studies to have precise results for this population.

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Authors' contributions

TA designed the study and NRG analyzed the results and MK and MKA performed and wrote the draft.

Availability of data and materials

Readers can reach the data and materials through direct contact to correspond author's email.

Consent for publication

Not applicable.

Declaration of competing interest

There is no conflict of interest.

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References

[1] Helvaci N, Eyupoglu ND, Karabulut E, Yildiz BO. Prevalence of obesity and its impact on outcome in patients with COVID-19: a systematic review and meta-analysis. Front Endocrinol 2021;12:82.
[2] Kheirvari M, Akbarzadeh I, Eshghjoo S, Yazdannasab M, Alaniz RC, Hosseini S, et al. Diagnostic value of erythrocyte sedimentation rate levels as a predictor of staple-line leakage in bariatric surgery. Bariatr Surg Pract Patient Care 2020 Dec;15(4):231–5.
[3] Amiki M, Seki Y, Kasama K, Hashimoto K, Kitagawa M, Umezawa A, et al. Revisional bariatric surgery for insufficient weight loss and gastroesophageal reflux disease: our 12-year experience. Obes Surg 2020;30(5):1671–8.
[4] Gunstad J, Sanborn V, Hawkins M. Cognitive dysfunction is a risk factor for overeating and obesity. Am Psychol 2020;75(2):219.
[5] Kheirvari M, Nikroo ND, Jaafarinejad H, Farsimadan M, Eshghjoo S, Hosseini S, et al. The advantages and disadvantages of sleeve gastrectomy; clinical laboratory to bedside review. Heliyon 2020;6(2):e03496.
[6] Sanborn VE, Spitznagel M-B, Crosby R, Steffen K, Mitchell J, Gunstad J. Cognitive function and quality of life in bariatric surgery candidates. Surg Obes Relat Dis 2018;14(9):1396–401.
[7] Rochette AD, Spitznagel MB, Strain G, Devlin M, Crosby RD, Mitchell JE, et al. Mild cognitive impairment is prevalent in persons with severe obesity. Obesity 2016;24(7):1427–9.
[8] Prehn K, Profitlich T, Rangus I, Heßler S, Witte AV, Grittner U, et al. Bariatric surgery and brain health—a longitudinal observational study investigating the effect of surgery on cognitive function and Gray matter volume. Nutrients 2020;12(1):127.
[9] Keshava HB, Mowla A, Heinberg LJ, Schauer PR, Brethauer SA, Aminian A. Bariatric surgery may reduce the risk of Alzheimer's diseases through GLP-1 mediated neuroprotective effects. Med Hypotheses 2017;104:4–9.
[10] Nota MHC, Vreeken D, Wiesmann M, Aarts EO, Hazebroek EJ, Kiliaan AJ. Obesity affects brain structure and function-rescue by bariatric surgery? Neurosci Biobehav Rev 2020;108:646–57.
[11] Kacířová M, Zmeškalová A, Kořínková L, Železná B, Kuneš J, Maletínská L. Inflammation: major denominator of obesity, Type 2 diabetes and Alzheimer's disease-like pathology? Clin Sci 2020;134(5):547–70.
[12] Mughal A, Harraz OF, Gonzales AL, Hill-Eubanks D, Nelson MT. PIP2 improves cerebral blood flow in a mouse model of Alzheimer's disease. Function 2021;2(2):zqab010.
[13] Howick K, Griffin BT, Cryan JF, Schellekens H. From belly to brain: targeting the ghrelin receptor in appetite and food intake regulation. Int J Mol Sci 2017;18(2):273.
[14] Beddows CA, Dodd GT. Insulin on the brain: the role of central insulin signalling in energy and glucose homeostasis. J Neuroendocrinol 2021:e12947.
[15] Pannacciulli N, Le DSNT, Chen K, Reiman EM, Krakoff J. Relationships between plasma leptin concentrations and human brain structure: a voxel-based morphometric study. Neurosci Lett 2007;412(3):248–53.
[16] Pannacciulli N, Del Parigi A, Chen K, Le DSNT, Reiman EM, Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. Neuroimage 2006;31(4):1419–25.
[17] Janowitz D, Wittfeld K, Terock J, Freyberger HJ, Hegenscheid K, Völzke H, et al. Association between waist circumference and gray matter volume in 2344 individuals from two adult community-based samples. Neuroimage 2015;122:149–57.
[18] Mathar D, Neumann J, Villringer A, Horstmann A. Failing to learn from negative prediction errors: obesity is associated with alterations in a fundamental neural learning mechanism. Cortex 2017;95:222–37.
[19] Tabasi M, Ashrafian F, Khezerloo JK, Eshghjoo S, Behrouzi A, Javadinia SA, et al. Changes in gut microbiota and hormones after bariatric surgery: a bench-to-bedside review. Obes Surg 2019 Feb;29(5):1663–74.
[20] Carranza-Naval MJ, Vargas-Soria M, Hierro-Bujalance C, Baena-Nieto G, Garcia-Alloza M, Infante-Garcia C, et al. Alzheimer's disease and diabetes: role of diet, microbiota and inflammation in preclinical models. Biomolecules 2021;11(2):262.
[21] Guo M, Peng J, Huang X, Xiao L, Huang F, Zuo Z. Gut microbiome features of Chinese patients newly diagnosed with Alzheimer's disease or mild cognitive impairment. J Alzheim Dis 2021;(Preprint):1–12.
[22] Hammond TC, Xing X, Wang C, Ma D, Nho K, Crane PK, et al. β-amyloid and tau drive early Alzheimer's disease decline while glucose hypometabolism drives late decline. Commun Biol 2020;3(1):1–13.
[23] Zhang M, Zhao D, Zhou G, Li C. Dietary pattern, gut microbiota, and Alzheimer's disease. J Agric Food Chem 2020;68(46):12800–9.
[24] Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 2003;163(13):1524–8.
[25] Kleinridders A, Ferris HA, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. Diabetes 2014;63(7):2232–43.
[26] Kiliaan AJ, Arnoldussen IAC, Gustafson DR. Adipokines: a link between obesity and dementia? Lancet Neurol 2014;13(9):913–23.
[27] Andreu S-S, Ibarra M, Libran M, Valverde M, Perea V, Luis G-P, et al. Role of sarcopenia in cognitive function in patients with morbid obesity before bariatric surgery. In: Endocrine abstracts. Bioscientifica; 2021.
[28] Kullmann S, Schweizer F, Veit R, Fritsche A, Preissl H. Compromised white matter integrity in obesity. Obes Rev 2015;16(4):273–81.
[29] Handley JD, Williams DM, Caplin S, Stephens JW, Barry J. Changes in cognitive function following bariatric surgery: a systematic review. Obes Surg 2016;26(10):2530–7.
[30] Smith KR, Moran TH, Papantoni A, Speck C, Bakker A, Kamath V, et al. Short-term improvements in cognitive function following vertical sleeve gastrectomy and Roux-en Y gastric bypass: a direct comparison study. Surg Endosc 2020;34(5):2248–57.
[31] Haley AP, Alosco ML, Gunstad J. Surgical and non-surgical interventions for obesity in service of preserving cognitive function. Psychosom Med 2015;77(6):679.
[32] Alosco ML, Spitznagel MB, Strain G, Devlin M, Cohen R, Paul R, et al. Improved memory function two years after bariatric surgery. Obesity 2014;22(1):32–8.
[33] Tan BC, Park YS, Won Y, Lee S, Kang SH, Ahn S-H, et al. Preoperative nutritional deficiencies in bariatric surgery candidates in Korea. Obes Surg 2021;1–9.
[34] McGlennon TW, Buchwald JN, Pories WJ, Yu F, Roberts A, Ahnfeldt EP, et al. Bypassing TBI: metabolic surgery and the link between obesity and traumatic brain injury—a review. Obes Surg 2020:1–11.
[35] Bianciardi E, Raimondi G, Samela T, Innamorati M, Contini LM, Procenesi L, et al. Neurocognitive and psychopathological predictors of weight loss after bariatric surgery: a 4-year follow-up study. Front Endocrinol 2021:12.
[36] Laferrère B. Effect of gastric bypass surgery on the incretins. Diabetes Metab 2009;35(6):513–7.
[37] Wilson J, Docherty P, Stubbs R, Chase JG, Krebs J. Assessment of the dynamic insulin secretion and sensitivity test (DISST) pre and post gastric bypass surgery. Exp Clin Endocrinol Diabetes 2020;128:164–9. 03.
[38] Madsbad S, Holst JJ. GLP-1 as a mediator in the remission of type 2 diabetes after gastric bypass and sleeve gastrectomy surgery. Diabetes 2014;63(10):3172–4.
[39] Adachi Y, Ota K, Minami I, Yamada T, Watanabe T. Lower insulin secretion is associated with hippocampal and parahippocampal gyrus atrophy in elderly patients with type 2 diabetes mellitus. J Diabetes Investig 2021;12(10):1908–13.
[40] Zhang ZQ, Hölscher C. GIP has neuroprotective effects in Alzheimer and Parkinson's disease models. Peptides 2020;125:170184.
[41] Salles GN, Calió ML, Hölscher C, Pacheco-Soares C, Porcionatto M, Lobo AO. Neuroprotective and restorative properties of the GLP-1/GIP dual agonist DA-JC1 compared with a GLP-1 single agonist in Alzheimer's disease. Neuropharmacology 2020;162:107813.
[42] Frisardi V, Solfrizzi V, Capurso C, Imbimbo BP, Vendemiale G, Seripa D, et al. Is insulin resistant brain state a central feature of the metabolic-cognitive syndrome? J Alzheim Dis 2010;21:57–63.
[43] Ji C, Xue G-F, Li G, Li D, Hölscher C. Neuroprotective effects of glucose-dependent insulinotropic polypeptide in Alzheimer's disease. Rev Neurosci 2016;27(1):61–70.
[44] Zanchi D, Depoorter A, Egloff L, Haller S, Mählmann L, Lang UE, et al. The impact of gut hormones on the neural circuit of appetite and satiety: a systematic review. Neurosci Biobehav Rev 2017;80:457–75.
[45] Sanborn V, Gunstad J. The potential mediation of the effects of physical activity on cognitive function by the gut microbiome. Geriatrics 2020;5(4):63.
[46] Morales-Marroquin E, Hanson B, Greathouse L, de la Cruz-Munoz N, Messiah SE. Comparison of methodological approaches to human gut microbiota changes in response to metabolic and bariatric surgery: a systematic review. Obes Rev 2020;21(8):e13025.
[47] Uysal G, Ozturk M. Hippocampal atrophy based Alzheimer's disease diagnosis via machine learning methods. J Neurosci Methods 2020;337:108669.
[48] Shen H, Guan Q, Zhang X, Yuan C, Tan Z, Zhai L, et al. New mechanism of neuroinflammation in Alzheimer's disease: the activation of NLRP3 inflammasome

mediated by gut microbiota. Prog Neuro-Psychopharmacol Biol Psychiatry 2020; 100:109884.
[49] Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Front Aging Neurosci 2016;8:256.
[50] Ulker I, Yildiran H. The effects of bariatric surgery on gut microbiota in patients with obesity: a review of the literature. Biosci Microbiota Food Health 2019;38(1): 3.
[51] Zhuang Z-Q, Shen L-L, Li W-W, Fu X, Zeng F, Gui L, et al. Gut microbiota is altered in patients with Alzheimer's disease. J Alzheim Dis 2018;63(4):1337–46.
[52] Sánchez-Alcoholado L, Gutiérrez-Repiso C, Gómez-Pérez AM, García-Fuentes E, Tinahones FJ, Moreno-Indias I. Gut microbiota adaptation after weight loss by Roux-en-Y gastric bypass or sleeve gastrectomy bariatric surgeries. Surg Obes Relat Dis 2019;15(11):1888–95.
[53] Palleja A, Kashani A, Allin KH, Nielsen T, Zhang C, Li Y, et al. Roux-en-Y gastric bypass surgery of morbidly obese patients induces swift and persistent changes of the individual gut microbiota. Genome Med 2016;8(1):67.
[54] Lu C, Li Y, Li L, Kong Y, Shi T, Xiao H, et al. Alterations of serum uric acid level and gut microbiota after roux-en-Y gastric bypass and sleeve gastrectomy in a hyperuricemic rat model. Obes Surg 2020;33(3):e2857.
[55] Damms-Machado A, Mitra S, Schollenberger AE, Kramer KM, Meile T, Königsrainer A, et al. Effects of surgical and dietary weight loss therapy for obesity on gut microbiota composition and nutrient absorption. BioMed Res Int 2015:1–12. 806248.
[56] Stanek KM, Gunstad J. Can bariatric surgery reduce risk of Alzheimer's disease? Prog Neuro-Psychopharmacol Biol Psychiatry 2013;47:135–9.
[57] Li C, Cai Y-Y, Yan Z-X. Brain-derived neurotrophic factor preserves intestinal mucosal barrier function and alters gut microbiota in mice. Kaohsiung J Med Sci 2018;34(3):134–41.
[58] Davies NK, O'Sullivan JM, Plank LD, Murphy R. Altered gut microbiome after bariatric surgery and its association with metabolic benefits: a systematic review. Surg Obes Relat Dis 2019;15(4):656–65.
[59] Kellerer T, Brandl B, Büttner J, Lagkouvardos I, Hauner H, Skurk T. Impact of laparoscopic sleeve gastrectomy on gut permeability in morbidly obese subjects. Obes Surg 2019;29(7):2132–43.
[60] Paganelli FL, Luyer M, Hazelbag CM, Uh HW, Rogers MRC, Adriaans D, et al. Roux-Y Gastric Bypass and Sleeve Gastrectomy directly change gut microbiota composition independent of surgery type. Sci Rep 2019;9(1):1–8.
[61] Karami R, Kermansaravi M, Pishgahroudsari M, Talebi M, Mohammadzadeh N, Pazouki A. Changes in gut microbial flora after Roux-en-Y gastric bypass and sleeve gastrectomy and their effects on post-operative weight loss. Updates Surg 2020; 73(4):1493–9.
[62] Liu R, Hong J, Xu X, Feng Q, Zhang D, Gu Y, et al. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. Nat Med 2017;23(7):859–68.
[63] Kong LC, Tap J, Aron-Wisnewsky J, Pelloux V, Basdevant A, Bouillot JL, et al. Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. Am J Clin Nutr 2013; 98(1):16–24.