


## Mechanisms of bariatric surgery in control of type 2 diabetes and Alzheimer's diseases: GLP-1 is the key factor-Maybe

Gholamreza Mohammadi Farsani<sup>1</sup>, Reza Yaghubi-tabar<sup>2</sup>, Taiebeh Mohammadi Farsani<sup>3\*</sup> 

Received: Feb 01, 2021/ Published Online: Feb 17, 2021

### Introduction

Obesity is the primary cause of hyperinsulinemia, which potentiates insulin resistance that may trigger type 2 diabetes (T2D) and increases the risk for dementia (1-3).

Globally, the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death. About 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM). Asia is a major area of the rapidly emerging T2DM global epidemic, with China and India the top two epicenters (4).

The prevalence and incidence of dementia increase exponentially from the age of 65 onwards. As a consequence of the progressive aging of the population and the increase in life expectancy, the number of cases of dementia will increase in the coming decades. Recent studies point to a slight drop in the accumulated risk of dementia adjusted by age groups and sex over the last few decades in some countries (5). Obesity associated with a higher risk for dementia (6).

Bariatric surgery may help to diminish Alzheimer's disease risk, while offering other health benefits to patients with severe obesity. Similarly, metabolic surgery in diabetic non-obese patients might delay the onset of Alzheimer's disease in addition to providing glycemic control (7).

Surgery is an effective treatment of type 2 diabetes mellitus in obese patients. The most optimal surgical procedure for the treatment of obese patients with type 2 diabetes mellitus is still to be established. More research is needed to explore the mechanisms of glycemic control after bariatric surgery (8).

We reviewed the effect of molecular pathway of bariatric surgery on T2DM and Alzheimer remission that is likely to be related to increased production of the incretin hormone, GLP-1. So that it is important to increase GLP-1 receptor agonists (GLP-1RAs) as a complementary pathway for bariatric surgery.

Obesity is the primary cause of hyperinsulinemia, which potentiates insulin resistance that may trigger type 2 diabetes (T2D) and increases the risk for dementia (1-3).

Globally, the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death. About 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM). Asia is a major area of the rapidly emerging T2DM global epidemic, with China and India the top two epicenters (4).

The prevalence and incidence of dementia increase exponentially from the age of 65 onwards. As a consequence of the progressive aging of the population and the increase in life expectancy, the number of cases of dementia will increase in the coming decades. Recent studies point to a slight drop in the accumulated risk of dementia adjusted by age groups and sex over the last few decades in some countries (5). Obesity associated with a higher risk for dementia (6).

Bariatric surgery may help to diminish Alzheimer's disease risk, while offering other health benefits to patients with severe obesity. Similarly, metabolic surgery in diabetic non-obese patients might delay the onset of Alzheimer's disease in addition to providing glycemic control (7).

Surgery is an effective treatment of type 2 diabetes mellitus in obese patients. The most optimal surgical procedure for the treatment of obese patients with type 2 diabetes mellitus is still to be established. More research is needed to explore the mechanisms of glycemic control after bariatric surgery (8).

We reviewed the effect of molecular pathway of bariatric surgery on T2DM and Alzheimer remission that is likely to be related to increased production of the incretin hormone, GLP-1. So that it is important to increase GLP-1 receptor agonists (GLP-1RAs) as a complementary pathway for bariatric surgery.

### Methods

Obesity is the primary cause of hyperinsulinemia, which potentiates insulin resistance that may trigger type 2 diabetes (T2D) and increases the risk for dementia (1-3).

Globally, the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death. About 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM). Asia is a

1. MD, MPH, PhD, Assistant Professor of Nutrition, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran. Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran, Email: mohammadigh53@gmail.com

2. Department of Medical Biotechnology, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran

3. Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

\* Taiebeh Mohammadi Farsani, [tmfarsani@gmail.com](mailto:tmfarsani@gmail.com)

major area of the rapidly emerging T2DM global epidemic, with China and India the top two epicenters (4).

The prevalence and incidence of dementia increase exponentially from the age of 65 onwards. As a consequence of the progressive aging of the population and the increase in life expectancy, the number of cases of dementia will increase in the coming decades. Recent studies point to a slight drop in the accumulated risk of dementia adjusted by age groups and sex over the last few decades in some countries (5). Obesity associated with a higher risk for dementia (6).

Bariatric surgery may help to diminish Alzheimer's disease risk, while offering other health benefits to patients with severe obesity. Similarly, metabolic surgery in diabetic non-obese patients might delay the onset of Alzheimer's disease in addition to providing glycemic control (7).

Surgery is an effective treatment of type 2 diabetes mellitus in obese patients. The most optimal surgical procedure for the treatment of obese patients with type 2 diabetes mellitus is still to be established. More research is needed to explore the mechanisms of glycemic control after bariatric surgery (8).

We reviewed the effect of molecular pathway of bariatric surgery on T2DM and Alzheimer remission that is likely to be related to increased production of the incretin hormone, GLP-1. So that it is important to increase GLP-1 receptor agonists (GLP-1RAs) as a complementary pathway for bariatric surgery.

## Results

Obesity continues to be a worldwide health problem in the twenty-first century. Bariatric surgery is a safe and effective long-term treatment for severe obesity that results in long-term weight loss, improvement and remission of obesity-related comorbid conditions (particularly T2DM and Alzheimer disease), improvement in quality of life and prolonged survival. New minimally invasive procedures, endoscopic devices and lower BMI indications will probably increase the adoption of the surgical treatments for patients with obesity.(9)

Studies show bariatric surgery as an effective treatment of type 2 diabetes mellitus in obese patients. The most optimal surgical procedure for the treatment of obese patients with type 2 diabetes mellitus is still to be established. More research is needed to explore the mechanisms of glycemic control after bariatric surgery (8, 9). Also Bariatric surgery may reduce the risk of Alzheimer's diseases (7).

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that binds to GLP-1 receptors mainly expressed on pancreatic beta-cells and the gastrointestinal system, which are G-protein coupled receptors (10). Largely from pre-clinical models, but data from patients as well, support a role of the postprandial rise in GLP-1 as driving the increased insulin and decreased glucose response to a meal. Less, clear is the extent to which GLP-1 changes are responsible for T2DM resolution.(11)

A systematic review e on the management of postoperative GLP-1 analogue usage after metabolic surgery re-

vealed that GLP-1 analogues may have beneficial effects on additional weight loss and T2D remission postoperatively (12).

GLP-1 receptors are also found in the brain (13). GLP-1 in the brain, similar to insulin, is principally a growth factor that increases cell growth, proliferation, and repair and inhibits apoptosis (14). GLP-1 protects against excitotoxic cell death and induces neurite outgrowth and oxidative injury in cultured neuronal cells (15).

So that bariatric surgery may reduce the risk of Alzheimer's diseases through GLP-1 mediated neuroprotective effects (7). Svane et al showed that food intake increased with combined blockade of GLP-1 and peptide YY (PYY) actions after RYGB. This study support that these hormones have a role in decreased food intake postoperatively.(16). Guida et al (2018) investigated changes in pancreatic PYY in diabetes and following RYGB. RYGB strongly increased islet PYY content, but did not lead to full restoration of pancreatic GLP-1 levels. Proteolytic enzyme dipeptidyl peptidase IV (DPP-IV) Modulate islet PYY. DPP-IV inhibition or RYGB caused Local regulation of pancreatic PYY that can directly modulate the insulin secretory response to glucose and indicate a novel role of pancreatic PYY in diabetes and weight-loss surgery (17).

The effect of bariatric surgery upon weight loss is less clear. It is possible that the acute calorie restriction which occurs immediately post surgery, coupled with a beneficial hormonal milieu promotes weight loss which, unusually, can be maintained over the long-term. This may, at least in part, be related to sustained increases in satiety-promoting peptides (GLP-1, glucose-dependent insulinotropic hormone, PYY3-36, oxyntomodulin, gastrin) and reductions in hunger-promoting factors (ghrelin) (18)

GLP-1RAs are approved for treating T2DM (19, 20). As a drug class, GLP-1RAs have proven efficacy for lowering glycated haemoglobin (HbA1c) and decreasing weight in T2DM, with a reduced risk of hypoglycaemia compared with insulin (Table 1) (20).

*Conflicts of Interest:* The authors declared no conflict of interest

*Funding:* None

*This work has been published under CC BY-NC-SA 4.0 license.*

Copyright© [Iran University of Medical Sciences](http://annbsurg.iums.ac.ir)

*Cite this article as:* Mohammadi Farsani GH, Yaghubi-tabar R, Mohammadi Farsani T. Mechanisms of bariatric surgery in control of type 2 diabetes and Alzheimer's diseases: GLP-1 is the key factor- Maybe. *Ann Bariatr Surg.* 2020(May);9(1).7.

**Table 1.** Some drug as GLP-1 receptor agonists and Percentage amino acid sequence similarity to native GLP-1

	Exenatide twice daily	Exenatide once weekly	Liraglutide once daily	Albiglutide once weekly	Dulaglutide once weekly	Taspoglutide once weekly
Properties of the drug	Resistant to DPP-4 cleavage, largely due to the substitution of alanine in position 2 by glycine (22)	Encapsulated in biodegradable polymer microspheres (23)	C-16 fatty acid confers albumin binding and heptamer formation (24)	GLP-1 dimer fused to albumin(25)	The GLP-1 portion of the molecule is fused to an IgG4 molecule, limiting renal clearance and prolonging activity (26)	Modifications designed to hinder cleavage by DPP-4 and by serine proteases and also allows greater receptor binding (27)
Percentage amino acid sequence similarity to native GLP-1	53%(28)	53%(28)	97%(24)	95%(25)	90% (26)	93%(27)

## References

- Halpern B, Mendes TB. Intermittent fasting for obesity and related disorders: unveiling myths, facts, and presumptions. *Archives of Endocrinology and Metabolism*. 2021(AHEAD).
- Rebelos E, Bucci M, Karjalainen T, Oikonen V, Bertoldo A, Hannukainen JC, et al. Insulin Resistance Is Associated With Enhanced Brain Glucose Uptake During Euglycemic Hyperinsulinemia: A Large-Scale PET Cohort. *Diabetes Care*. 2021.
- Kanety H, Moshe S, Shafir E, Lunenfeld B, Karasik A. Hyperinsulinemia induces a reversible impairment in insulin receptor function leading to diabetes in the sand rat model of non-insulin-dependent diabetes mellitus. *Proceedings of the National Academy of Sciences*. 1994;91(5):1853-7.
- Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology*. 2018;14(2):88.
- Garre-Olmo J. Epidemiology of Alzheimer's disease and other dementias. *Revista de neurologia*. 2018;66(11):377-86.
- Stephens K. Obesity May Exacerbate the Effects of Alzheimer's Disease, MRI Research Shows. *AXIS Imaging News*. 2021.
- 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. *Medical hypotheses*. 2017;104:4-9.
- Maleckas A, Venclauskas L, Wallenius V, Lönroth H, Fändriks L. Surgery in the treatment of type 2 diabetes mellitus. *Scandinavian Journal of Surgery*. 2015;104(1):40-7.
- Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. *Nature reviews Gastroenterology & hepatology*. 2017;14(3):160.
- Green B, Gault V, Flatt P, Harriott P, Greer B, O'Harte F. Comparative effects of GLP-1 and GIP on cAMP production, insulin secretion, and in vivo antidiabetic actions following substitution of Ala8/Ala2 with 2-aminobutyric acid. *Archives of biochemistry and biophysics*. 2004;428(2):136-43.
- Hutch CR, Sandoval D. The role of GLP-1 in the metabolic success of bariatric surgery. *Endocrinology*. 2017;158(12):4139-51.
- Schneider R, Kraljević M, Peterli R, Rohm TV, Klasen JM, Cavelti-Weder C, et al. GLP-1 Analogues as a Complementary Therapy in Patients after Metabolic Surgery: a Systematic Review and Qualitative Synthesis. *Obesity Surgery*. 2020;30:3561-9.
- Hamilton A, H ölscher, C.(2009) Receptors for the insulin-like peptide GLP-1 are expressed on neurons in the CNS. *NeuroReport*.20:1161-6.
- Perfetti R, Zhou J, Doyle MiE, Egan JM. Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenum homeobox-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. *Endocrinology*. 2000;141(12):4600-5.
- Perry T, Lahiri DK, Sambamurti K, Chen D, Mattson MP, Egan JM, et al. Glucagon-like peptide-1 decreases endogenous amyloid- $\beta$  peptide (A $\beta$ ) levels and protects hippocampal neurons from death induced by A $\beta$  and iron. *Journal of neuroscience research*. 2003;72(5):603-12.
- Svane M, Jørgensen NB, Bojsen-Møller K, Dirksen C, Nielsen S, Kristiansen V, et al. Peptide YY and glucagon-like peptide-1 contribute to decreased food intake after Roux-en-Y gastric bypass surgery. *International Journal of Obesity*. 2016;40(11):1699.
- Guida C, McCulloch LJ, Godazgar M, Stephen SD, Baker C, Basco D, et al. Sitagliptin and Roux-en-Y gastric bypass modulate insulin secretion via regulation of intra-islet PYY. *Diabetes, Obesity and Metabolism*. 2018;20(3):571-81.
- Meek CL, Lewis HB, Reimann F, Gribble FM, Park AJ. The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones. *Peptides*. 2016;77:28-37.
- Urquhart S, Willis S. Long-acting GLP-1 receptor agonists: Findings and implications of cardiovascular outcomes trials. *Journal of the American Academy of PAs*. 2020;33(S8):19-30.
- Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. *Diabetes, Obesity and Metabolism*. 2016;18(4):317-32.
- Cătoi AF, Părvu A, Mureșan A, Busetto L. Metabolic mechanisms in obesity and type 2 diabetes: insights from bariatric/metabolic surgery. *Obesity facts*. 2015;8(6):350-63.
- Donnelly D. The structure and function of the glucagon-like peptide-1 receptor and its ligands. *British journal of pharmacology*. 2012;166(1):27-41.
- DeYoung MB, MacConell L, Sarin V, Trautmann M, Herbert P. Encapsulation of exenatide in poly-(D, L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. *Diabetes technology & therapeutics*. 2011;13(11):1145-54.
- Sjöholm Å. Liraglutide therapy for type 2 diabetes: overcoming unmet needs. *Pharmaceuticals*. 2010;3(3):764-81.
- Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes care*. 2011;34(Supplement 2):S279-S84.
- Qie S, Li X, Wang X, Liu Y, Li J, Liu G. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonist dulaglutide in patients with type 2 diabetes: a systematic review and meta-analysis of 21 randomized controlled trials. *Endocrine*. 2020;68(3):508-17.
- Linderth L, Kofoed J, Kodra JT, Reedtz-Runge S, Kruse T. GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes and Obesity. *Successful Drug Discovery, Volume 5*. 2021.
- Vestlund J, Jerlhag E. The glucagon-like peptide-1 receptor agonist, exendin-4, reduces sexual interaction behaviors in a brain site-specific manner in sexually naïve male mice. *Hormones and Behavior*. 2020;124:10