

CASE REPORT

Investigating GLP-1 Injections: Potential Mitochondrial Dysfunction in Non-Diabetic Patients Presenting with Migraines and Hypoglycemia: A Case Report

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Abstract

Introduction • GLP-1 medications are widely used for weight loss in patients with and without type 2 diabetes. However, limited research exists on their effects in non-diabetic patients, particularly concerning mitochondrial function. This case report investigates the potential of altered mitochondrial dysfunction as a cause of side effects of GLP-1 medications in patients without type 2 diabetes.

Case Presentation • The patient, a 43-year-old female with a BMI of 32, presented with hypoglycemia and persistent migraines with auras after Ozempic and Mounjaro injections.

Outcomes • The patient changed her diet to include 90 grams of protein and frequent small meals throughout the day. She took CoQ10, D-ribose, vitamin B complex,

and acetyl-L-carnitine, to address the migraines, and this also improved the mitochondrial function. The patient reported balanced blood sugar after changing her diet; her migraines improved and did not return after taking supplementation.

Conclusion • This case report emphasizes the need for awareness and monitoring of potential mitochondrial side effects from GLP-1 injections in patients without type 2 diabetes. Nutritional and supplemental interventions effectively managed the patient's symptoms and emphasized the need for tailored interventions in patients using GLP-1 medications. Further research is needed to understand how GLP-1 injections impact mitochondrial function.

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Introduction

Glucagon-Like Peptide-1 (GLP-1) medications have dramatically increased in popularity as weight loss drugs for patients with and without type 2 diabetes. Semaglutide GLP-1 use has increased since 2022, with over 9 million prescriptions written.¹ Patients without diabetes are also

utilizing these drugs for weight loss when diet and exercise prove ineffective.¹ Semaglutide, Ozempic, and Mounjaro are GLP-1 mimics that decrease blood glucose levels, change gastric emptying time, reduce cravings, and increase satiety.²⁻⁴ GLP-1 medications are prescribed as a once-weekly subcutaneous injection of 2.4-3.0 mg, depending on symptoms.²⁻⁴

GLP-1 injections were originally used to improve the health of patients with type 2 diabetes. These patients have altered mitochondrial function from decreased insulin sensitivity, and GLP-1 agonists can improve and restore mitochondrial function.⁵⁻⁹ GLP-1 agonists' impact on metabolic and mitochondrial function has been studied extensively in patients with type 2 diabetes, demonstrating improvements in blood glucose levels, insulin sensitivity, pancreatic beta cell function, and mitochondrial function through mitochondrial uncoupling.⁵⁻⁹ In non-diabetic patients with obesity, GLP-1 agonists improve mitochondrial respiration, mitogenesis, and inflammation, and increase the number of mitochondria in adipose tissue, but there is limited research on how GLP-1 affects mitochondria in other tissues in this patient population.¹⁰

Undesirable side effects can accompany GLP-1 medications, and as many as 84% of patients may experience gastrointestinal disorders such as diarrhea,

nausea, vomiting, unpleasant burps, gastroesophageal reflux disease (GERD), and peptic ulcers.^{11,12} In non-diabetic patients, hypoglycemia and headache have been reported in up to 10-21% of patients after taking GLP-1.¹³ Hypoglycemia could indicate altered mitochondrial function from medically reduced glucagon levels.¹⁴ The mechanism and cause of headache were not examined, and migraines were not mentioned.¹³ Migraines are not commonly reported as a side effect of GLP-1 medications, and an animal study has shown that liraglutide GLP-1 injections can improve migraine symptoms by increasing IL-10 levels.^{15,16} Migraine pathogenesis could be attributed to altered mitochondrial function in neurons from GLP-1 agonists, however, this topic is underexplored.

Non-diabetic patients taking GLP-1 injections may infrequently experience side effects such as migraines and hypoglycemia, which could indicate altered mitochondrial function in pancreatic alpha and neuron cells. This case explores the potential mechanisms behind migraines-associated headaches as a side effect in non-diabetic patients taking GLP-1 injections for weight loss, with a focus on alteration in mitochondrial function.

Case Narrative

A 43-year-old female with a body mass index (BMI) of 32, fasting blood glucose of 80 mg/dL, and HbA_{1c} % of 5.2 indicating obesity and non-diabetes, sought nutritional and supplemental support from a nutritionist to increase her energy and address the side effects from her Ozempic prescription, including nausea and hypoglycemia. The patient’s past medical history was significant for weight gain following pregnancy and occasional migraines with aura. She was taking Lexapro, Synthroid, Gabapentin, and Pantoprazole for acid reflux, and had followed a vegan and vegetarian diet for 16 years.

The patient was prescribed 0.5 mg of Ozempic by her physician in April 2023. After the patient reported adverse side effects of chronic nausea and hypoglycemia her Ozempic dose was decreased to 0.25 mg. Her physician recommended her to wear a glucose monitor in the

evenings to wake her if her blood glucose became dangerously low. The patient reported suboptimal protein intake and eating infrequent meals throughout the day due to her job on a dietary recall form.

After six months, in October 2023, the patient’s physician changed to 0.15 mg of Mounjaro to mitigate her chronic nausea. In January 2024, three months after taking 0.15 mg of Mounjaro, the patient reported regular migraine occurrence, and shoulder, hip, and body pain. The migraine symptoms included dizziness, scalp pain, auras, vision changes, misremembering words, and pain on the left side of her head. The patient has had infrequent aura migraines beginning in 2018 but experienced new migraine symptoms after Mounjaro injections.

Diagnostic Assessment

The patient was diagnosed with hypoglycemia and recommended to wear a continuous glucose monitor. The nutritionist identified suboptimal protein intake based on the patient’s dietary recall form. Further, the form indicated infrequent meals and ingesting high glycemic foods. No imaging or workup was done for the migraine presentation.

Therapeutic Intervention

In April 2023, the nutritionist recommended a diet with 90 grams of protein daily to improve hypoglycemia.¹⁷ The nutritionist recommended small frequent meals throughout the day and the removal of high glycemic processed foods to maintain her blood glucose levels.¹⁸ In January 2024, regular migraine occurrence was noted by the patient, this was the first speculation that the GLP-1 medication could alter mitochondrial function, rather than being triggered by hypoglycemia. The nutritionist recommended 300 mg of CoQ10 per day, 4250 mg of D-ribose per day, vitamin B complex once per day, and 500 mg of acetyl-L-carnitine per day to address the migraines.¹⁹⁻²² The patient reported nausea as an adverse side effect of acetyl-L-carnitine and discontinued the supplement after two weeks.

Outcomes

In April 2023, two weeks after the patient changed her diet to include 90 grams of protein per day and eating regularly throughout the day her, blood glucose levels stabilized as evidenced by the cessation of the glucose monitor waking her during the night. After two weeks she no longer needed to wear the blood glucose monitor. Hypoglycemia was addressed through protein and regular meals.^{9,10,23} The patient continued the diet after changing to Mounjaro in October 2023. In January 2024, the patient began taking CoQ10, D-ribose, and vitamin B complex and reported her migraine symptoms had gone away within 48 hours of starting the supplements. The patient continued taking CoQ10, D-ribose, and vitamin B complex and her migraine symptoms did not return.

Table 1. Timeline of patient’s nutrition interventions

	Intervention	Rationale
04/2023	90 grams of lean protein daily. 20-30 grams of protein at dinner. Frequent small meals eaten throughout the day	Improve hypoglycemia. ¹⁶⁻¹⁷
01/2024	Methylated vitamin B complex once per day	Increase absorption of vitamin B12 and improve migraines. ¹³
	300 mg CoQ10 once per day with high fiber meal	Improve migraines. ^{16,18-19}
	500 mg Acetyl-L-carnitine once per day	
	4250 mg D-ribose once per day with a high fiber meal	Improve fatigue. ²⁰

Discussion

The discussion below delineates the potential role of altered mitochondrial function in the onset of migraine headaches in patients taking GLP-1 injections. Migraines and hypoglycemia are possible indicators of increased mitochondrial ATP synthesis and signaling in pancreatic alpha cells and neurons.

Mitochondrial Function

The patient's side effects may be associated with altered mitochondrial function, specifically regarding the pancreatic alpha mitochondria and activity rate in the neuronal electron transport chain.

Hypoglycemia

GLP-1 medications decrease blood glucose, and the patient reported hypoglycemia while taking Ozempic but not Mounjaro.² The patient reported having hypoglycemia at night and wore a glucose monitor to wake her up if her glucose levels dropped too low. Her glucose monitor woke her up three times. When she implemented the high-protein diet her monitor no longer woke her to indicate dangerously low glucose levels.

GLP-1 agonists inhibit glucagon from the alpha cells in the pancreas, which is essential for maintaining blood glucose levels by signaling the liver to convert glycogen through glycogenolysis and into the bloodstream to increase glucose levels and maintain blood sugar.^{5,7} GLP-1 agonists may inhibit the signal from alpha cell mitochondria to release glucagon and therefore increase the risk of hypoglycemia because the body cannot naturally stabilize blood sugar levels.^{5,7} This could increase the risk of hypoglycemia in non-diabetic patients with healthy blood sugar levels, as the patient in this case report did, but this is speculative.⁸ In a clinical trial on obese patients taking varying doses of semaglutide and liraglutide, patients who took 0.3-0.4 mg of GLP-1 medications with and without fasting reported the highest amount of headaches and hypoglycemia.¹³ The dose of GLP-1 medications could be a factor for both symptoms.¹³ Practitioners may need to consider prescribing a lower dose in non-diabetic patients with normal blood glucose levels to reduce the potential risk of hypoglycemia.¹³ Fasting also exacerbated hypoglycemia, and ingesting enough calories is essential for supporting this patient population.¹³ Research needs to be done to understand how GLP-1 medications affect pancreatic alpha cells in non-diabetic individuals to better support patients taking the drug.

Dietary Interventions

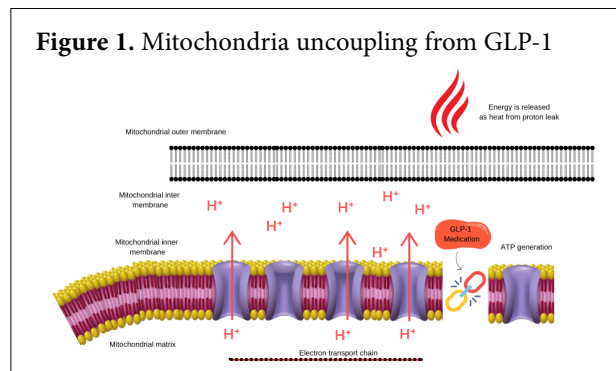
Before treatment, this patient followed a vegan and vegetarian diet for 16 years. She did not prioritize protein, which could have contributed to the severity of her hypoglycemic symptoms from Ozempic. She also did not eat regularly throughout the day and sometimes relied on ultra-processed snack foods between meetings.¹⁷ Patients

who ate four meals per day three to four hours apart saw a decrease in hypoglycemic symptoms, especially when the diet included nutrient-dense whole foods, although these patients were not taking GLP-1 medications.¹⁷ Since decreasing blood sugar is one of the main mechanisms of GLP-1 agonists, hypoglycemia was a concern for this patient. Eating 90 grams of protein daily is essential for maintaining blood sugar levels because protein increases glucagon and stabilizes blood sugar.^{17,18} The patient saw significant improvement in her hypoglycemia when she consistently ate throughout the day and when she ingested 20-30 grams of protein in the evenings from beans, tofu, turkey, fish, and eggs.

Speculated Migraine Triggers

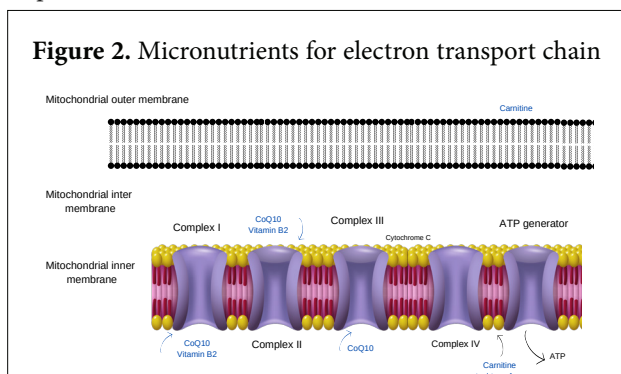
Hypoglycemia can contribute to migraines; however, hypoglycemia was addressed, and migraines still occurred. Under the influence of Exendin-4, another GLP-1 agonist medication from Gila monster saliva, mitochondria operate differently.²³ Protons leak across the mitochondrial membrane into the matrix, and this diverts energy from the electron transport chain to heat production; this process is called mitochondrial uncoupling (Figure 1).²⁴ Exendin-4 acts as an uncoupling agent which changes the metabolic rate and increases resting energy expenditure.²³ Exendin-4 also affects sirtuin enzymes, which regulate mitochondrial function, metabolism, and inflammation, and when increased from mitochondrial uncoupling, can potentially lead to migraines.²³ Ozempic and Mounjaro may also influence mitochondrial uncoupling in non-diabetic patients, which could increase the rate of ATP synthesis and contribute to migraines. However, more research needs to be done to determine how the GLP-1 agonists dissociate ATP synthesis in this patient population.

When observed during functional imaging, the medulla and hypothalamus are activated during migraine attacks.²⁴ As GLP-1 receptors are also found in the medulla and hypothalamus, these cells may have altered mitochondrial function following the use of GLP-1 medications.²⁴ GLP-1 receptors in the medulla and hypothalamus could receive too much GLP-1 hormone from Mounjaro injections, and ATP synthesis activity could increase from mitochondrial uncoupling, resulting in unbalanced reactive oxygen species.²⁵ A cross-sectional



study showed an increased rate of mitochondrial ATP synthesis leads to increased levels of reactive oxygen species, resulting in impaired mitochondrial function and the release of peptides hypoxia-inducible factor-1 α , fibroblast growth factor-21, calcitonin gene-related peptide, and pituitary adenylate cyclase-activating peptide-38 which can trigger migraines.²⁵ GLP-1 agonists could be causing mitochondrial uncoupling in the receptors in the medulla and hypothalamus in non-diabetic patients, which may increase ATP synthesis and migraines, but this is speculative.^{9,17,26} Migraines are not commonly reported from GLP-1 agonists, however, another case report included a patient presenting with hemiplegic migraines for over 60 days following GLP-1 injections.¹⁶ The case report did not mention mitochondrial function.¹⁶

Vitamin B2, CoQ10, and D-ribose are essential for mitochondrial function, particularly in the electron transport chain complexes one, two, and three (Figure 2).^{19,20,27} CoQ10 is an antioxidant and decreases oxidative stress by rebalancing oxidation in the mitochondria.²⁰ When the patient presented with regularly occurring migraine symptoms after changing medications, this was the first indication that GLP-1 injections could influence changes to mitochondrial activity in neurons, and micronutrient intervention may be necessary to support the electron transport chain. In an animal study, GLP-1 medications altered cholesterol metabolism and reduced cholesterol levels by reducing HMG-CoA reductase and SREBP-1C enzymes.²⁶ HMG-CoA reductase stimulates the synthesis of CoQ10, and if inhibited, CoQ10 levels drop, and energy production is disrupted as CoQ10 is required to initiate the electron transport chain.²³ If CoQ10 cannot be used for the electron transport chain and the rate of ATP synthesis increases from GLP-1 injections; this could alter mitochondrial function, and increase levels of reactive oxygen species, oxidative stress, and release peptides that could trigger migraines.^{20,24,26} D-ribose can improve ATP synthesis and cellular processing when the rate of the electron transport chain is altered or if there are missing enzymes that inhibit energy production.²⁷ D-ribose can bypass enzymatic pathways in the mitochondria and still generate ATP, which can improve mitochondrial function.²⁷



In this case study, the patient experienced relief from migraines after taking CoQ10, vitamin B complex, and D-ribose supplementation while on Mounjaro.^{18,20,22} GLP-1-induced alterations to mitochondrial and electron transport function, may have been resolved through supplementation. It is possible that Mounjaro impacted mitochondrial function, ultimately creating a deficit of CoQ10, and contributing to migraine occurrence. Upon CoQ10 supplementation, the energy balances and alterations in mitochondrial function were restored. Human studies need to be conducted to understand how GLP-1 medications interact with mitochondria in the medulla and hypothalamus and with HMG-CoA reductase.

Conclusion

The patient lost 40 pounds after one year of taking Ozempic and Mounjaro, resulting in a BMI of 25.8, and is no longer categorized as obese. She changed her diet to include 90 grams of protein, took the recommended supplements, and found these nutraceutical interventions were the most effective in alleviating medication-related migraine symptoms and hypoglycemia. Non-diabetic individuals with normal blood glucose levels may be at a greater risk of hypoglycemia and migraines from GLP-1 medications because of the speculated changes to mitochondrial function and the rate of ATP synthesis. Future research should explore the effects of GLP-1 agonists on mitochondrial function in neuronal and alpha pancreatic cells through in vitro and in vivo studies. Screening patients for migraine status may be necessary to evaluate the increased risk to benefit of prescribing GLP-1 medications.

Patient Perspective

The patient noted that while the high-protein diet was beneficial, the supplements that addressed her migraine symptoms were the most impactful. She appreciated targeted treatments based on her symptoms from Ozempic and Mounjaro.

Limitations

The patient submitted her diet through a form which increases the risk of reporting bias.

Author Disclosure Statement

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References

- 2023 trends shaping the Health Economy Report. Trilliant Health. 2023. Accessed June 26, 2024. <https://www.trillianthealth.com/hubfs/2023%20Trends%20Shaping%20the%20Health%20Economy%20Report.pdf>.
- Calanna S, Christensen M, Holst JJ, et al. Secretion of glucagon-like peptide-1 in patients with type 2 diabetes mellitus: systematic review and meta-analyses of clinical studies. *Diabetologia*. 2013;56(5):965-972. doi:10.1007/s00125-013-2841-0

3. Kadouh H, Chedid V, Halawi H, et al. GLP-1 Analog Modulates Appetite, Taste Preference, Gut Hormones, and Regional Body Fat Stores in Adults with Obesity. *J Clin Endocrinol Metab*. 2020;105(5):1552-1563. doi:10.1210/clinem/dgz140
4. Pirro V, Roth KD, Lin Y, et al. Effects of Tirzepatide, a Dual GIP and GLP-1 RA, on Lipid and Metabolite Profiles in Subjects With Type 2 Diabetes. *J Clin Endocrinol Metab*. 2022;107(2):363-378. doi:10.1210/clinem/dgab722
5. Buteau J. GLP-1 signaling and the regulation of pancreatic β -cells mass/function. *Avances en Diabetologia*. 2011;27(1):3-8. doi:10.1016/S1134-3230(11)70002-3
6. Kwak SH, Park KS, Lee KU, Lee HK. Mitochondrial metabolism and diabetes. *J Diabetes Investig*. 2010;1(5):161-169. doi:10.1111/j.2040-1124.2010.00047.x
7. Wang Y, Wang J, Tao S-Y, et al. Mitochondrial damage-associated molecular patterns: A new insight into metabolic inflammation in type 2 diabetes mellitus. *Diabetes Metab Res Rev*. 2024;40(2):e3733. doi:10.1002/dmrr.3733
8. Reed J, Bain S, Kanamarlapudi V. Recent advances in understanding the role of glucagon-like peptide 1. *F1000Res*. 2020;9:F1000 Faculty Rev-239. doi:10.12688/f1000research.20602.1
9. Góralaska J, Śliwa A, Gruca A, et al. Glucagon-like peptide-1 receptor agonist stimulates mitochondrial bioenergetics in human adipocytes. *Acta Biochim Pol*. 2017;64(3):423-429. doi:10.18388/abp.2017_1634
10. Vaittinen M, Ilha M, Herbers E, et al. Liraglutide demonstrates a therapeutic effect on mitochondrial dysfunction in human SGBS adipocytes in vitro. *Diabetes Res Clin Pract*. 2023;199:110635. doi:10.1016/j.diabres.2023.110635
11. Rubino DM, Greenway FL, Khalid U, et al; STEP 8 Investigators. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA*. 2022;327(2):138-150. doi:10.1001/jama.2021.23619
12. Tobaigy M, Elkout H. Psychiatric adverse events associated with semaglutide, liraglutide and tirzepatide: a pharmacovigilance analysis of individual case safety reports submitted to the EudraVigilance database. *Int J Clin Pharm*. 2024;46(2):488-495. doi:10.1007/s11096-023-01694-7
13. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392(10148):637-649. doi:10.1016/S0140-6736(18)31773-2
14. Ashfaq M, Moats AR, Northrup H, et al. Hypoglycemia in mitochondrial disorders. *Mitochondrion*. 2021;58:179-183. doi:10.1016/j.mito.2021.03.002
15. Jing F, Zou Q, Pu Y. GLP-1R agonist liraglutide attenuates pain hypersensitivity by stimulating IL-10 release in a nitroglycerin-induced chronic migraine mouse model. *Neurosci Lett*. 2023;812:137397. doi:10.1016/j.neulet.2023.137397
16. Modestino EJ, Bowirrat A, Lewandrowski K-U, et al. Hemiplegic Migraines Exacerbated using an Injectable GLP-1 Agonist for Weight Loss. *Acta Sci Neurol*. 2024;7(5):12-18. doi:10.31080/ASNE.2024.07.0731
17. Ichikawa R, Takano K, Fujimoto K, et al. Robust increase in glucagon secretion after oral protein intake, but not after glucose or lipid intake in Japanese people without diabetes. *J Diabetes Investig*. 2023;14(10):1172-1174. doi:10.1111/jdi.14053
18. Hall M, Walicka M, Panczyk M, Traczyk I. Assessing Long-Term Impact of Dietary Interventions on Occurrence of Symptoms Consistent with Hypoglycemia in Patients without Diabetes: A One-Year Follow-Up Study. *Nutrients*. 2022;14(3):497. doi:10.3390/nu14030497
19. Chen Y-S, Lee H-F, Tsai C-H, et al. Effect of Vitamin B2 supplementation on migraine prophylaxis: a systematic review and meta-analysis. *Nutr Neurosci*. 2022;25(9):1801-1812. doi:10.1080/1028415X.2021.1904542
20. Sazali S, Badrin S, Norhayati MN, Idris NS. Coenzyme Q10 supplementation for prophylaxis in adult patients with migraine-a meta-analysis. *BMJ Open*. 2021;11(1):e039358. doi:10.1136/bmjopen-2020-039358
21. Rossini M, Di Munno O, Valentini G, et al. Double-blind, multicenter trial comparing acetyl l-carnitine with placebo in the treatment of fibromyalgia patients. *Clin Exp Rheumatol*. 2007;25(2):182-188.
22. Teitelbaum JE, Johnson C, St Cyr J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. *J Altern Complement Med*. 2006;12(9):857-862. doi:10.1089/acm.2006.12.857
23. Jo D, Yoon G, Song J. Role of Exendin-4 in Brain Insulin Resistance, Mitochondrial Function, and Neurite Outgrowth in Neurons under Palmitic Acid-Induced Oxidative Stress. *Antioxidants*. 2021;10(1):78. doi:10.3390/antiox10010078
24. Charles A, Brennan KC. The neurobiology of migraine. *Handb Clin Neurol*. 2010;97:99-108. doi:10.1016/S0072-9752(10)97007-3
25. Kilinc YB, Kilinc E, Danis A, et al. Mitochondrial metabolism related markers GDF-15, FGF-21, and HIF-1 α are elevated in pediatric migraine attacks. *Headache*. 2023;63(8):1076-1086. doi:10.1111/head.14618
26. Farr OM, Sofopoulos M, Tsoukas MA, et al. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. *Diabetologia*. 2016;59(5):954-965. doi:10.1007/s00125-016-3874-y
27. Mahoney DE, Hiebert JB, Thimmesch A, et al. Understanding D-Ribose and Mitochondrial Function. *Adv Biosci Clin Med*. 2018;6(1):1-5. doi:10.7575/aic.abcmed.v6n1.p1