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Original article

Effect of Dulaglutide on HbA1c and Vit B12, on Alloxan-Induced Diabetes in Albino Mice

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Abstract
Diabetes mellitus (DM) is a metabolic disorder caused by a defect in insulin secretion, insulin action, or both; insufficient production of insulin results in prolonged elevated blood sugar levels. Insulin is initially synthesized in the beta cells of the pancreas as a larger single-chain polypeptide precursor known as proinsulin. Types of diabetes: primary and secondary. Primary diabetes is divided into types 1 and 2; type 1 is treated with insulin, while type 2 is treated with sulfonylureas, meglitinides, incretins, DPP-4 inhibitors, thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), insulin, and GLP-1 receptor agonists. Dulaglutide is a long-acting human GLP-1 receptor agonist. Its effects include glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and weight loss with metformin. 24 albino mice were obtained from the animal house University of Benghazi and kept breeding for the experiment, they were chosen according to their weight and ranged from 20-30gm g. Divided into 3 groups, group 1 takes a normal pallet diet, the other 2 groups received HFD for 2 weeks, then alloxan was injected into all groups except group 1. After that, measure blood sugar if more than 140 given drugs for group 3, Dulaglutide. Drugs are given for one month. After a month, mice were sacrificed, and HbA1c and vitamin B12 were investigated.
Keywords. Diabetes Mellitus, Insulin Resistance, Dulaglutide, GLP-1 Receptor Agonist, Alloxan-Induced Diabetes.

Introduction

Diabetes mellitus (DM) is a metabolic disease caused by a deficiency in either insulin secretion, insulin action or both. Insufficient insulin production leads to persistently high blood sugar levels, which affect the metabolism of proteins, lipids, and carbohydrates. As the disease progresses, it may impact several bodily tissues [1]. Insulin is first produced in the pancreatic beta cells as proinsulin, a bigger single-chain polypeptide precursor. During its storage in the beta cell, the single-chain proinsulin is cleaved, resulting in the removal of a connecting strand C-peptide and the appearance of the smaller, double-chain insulin molecule. Insulin and the C-peptide are bundled in membrane-bound storage granules, then travel toward the cell membrane and discharge their contents through a process of endocytosis and exocytosis, in which is fusion of the granule membrane fuses with the cell membrane [2]. The rising disease burden of diabetes mellitus internationally is a major public health problem. According to the most recent projections, 425 million people worldwide had diabetes in 2017; by 2045, that number is predicted to increase to 629 million. This is propelled by the global growth in the incidence of obesity and unhealthy behaviors, including poor diets and physical inactivity; these are in turn fostered by wider societal variables, including changes in nutrition in a global setting so so-called nutrition transition [3].

There are two types of diabetes: primary and secondary. Primary classified into type 1 and type 2 diabetes mellitus. Gestational diabetes, congenital diabetes, diabetes associated with cystic fibrosis, and steroid diabetes brought on by high glucocorticoid dosages are examples of secondary diabetes [4]. kind 1 DM or insulin-dependent diabetic mellitus (IDDM) or juvenile-onset diabetes originally comprised this kind of diabetes. Type 1 diabetes results from an autoimmune breakdown of the ß-cells of the pancreas. Body fluids and tissue include a number of indicators of this autoimmune damage [5]. Depending on whether hypoglycemia and hyperglycemia-related symptoms (including polyuria and thirst) are present or absent, the pathophysiology of type 1 diabetes can be separated into three stages [6]. Continuous hyperglycemia is responsible for the emergence of various organ and tissue damage in diabetic people. Eyes induce retinopathy, kidneys cause nephropathy, and peripheral nerves cause neuropathy. Diabetes-specific changes in microvessels cause frequent injury. Additionally, injury to major vessels results in serious illnesses such as gangrene, cerebral infarction, and myocardial infarction [7]. Management of type 1 predominantly by insulin through injections or using an insulin pump [6]. NIDDM, or type 2 non-insulin-dependent diabetic mellitus, is sometimes known as T2DM. One of the most prevalent metabolic illnesses is caused by a combination of two basic factors: faulty insulin secretion by pancreatic β-cells and the failure of insulin-sensitive tissues to respond correctly to insulin. Accelerated development of atherosclerosis is linked to type 2 diabetes [8].

Advances of the disease make insulin secretion unable to maintain glucose homeostasis, creating hyperglycemia. Patients with T2DM are generally characterized by being obese or having a greater body fat percentage, primarily in the abdominal region. In this state, adipose tissue increases IR (Insulin resistance through several inflammatory pathways, including increased free fatty acid (FFA) release and adipokine dysregulation [9]. The global increase in obesity, sedentary lifestyles, high-calorie meals, and population

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aging are the primary causes of the T2DM epidemic, which has doubled the incidence and prevalence of the disease [9, 10]. The organs involved in T2DM include the pancreas (β-cells and α-cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue [11]. Although metformin and lifestyle changes remain the mainstays of type 2 diabetes mellitus first treatment, a growing number of second and third-line pharmaceutical treatments are available. Sulphonyl-urease, insulin, thiazolidinedione, and alpha-glucosidase inhibitors are among them; more recently, glucagon-like peptide-1 agonists, dipeptidyl peptidase-IV inhibitors, and pramlintide have been included. Additionally, insulin mimics that more closely resemble endogenous insulin production have been created [12]. Sulfonylureas effective treatment plan to achieve blood glucose objectives when taken alone or in conjunction with other anti-hyperglycemic medicines. The most common use of this is in conjunction with metformin [13]. The most prevalent adverse effect limiting its usage is hypoglycemia, especially in elderly persons with reduced renal function, hepatic dysfunction [13].

GLP-1 receptor agonists

There have been many studies demonstrating the efficacy and side effects of GLP-1 receptor agonists, including exenatide and liraglutide, dulaglutide, but none are specifically intended for older persons with diabetes. However, there are no variations in the efficacy and safety profile between senior and younger individuals [14, 15]. Its action includes glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of stomach emptying, and weight loss [16]. It is a molecule comprised of two identical, disulfide-linked chains, each comprising an N-terminal GLP-1 analog sequence covalently attached to a modified human immunoglobulin IgG4 Fc (immunoglobulin fragment) heavy chain by a short peptide linker [17]. Unlike native GLP-1, dulaglutide is not broken down by dipeptidyl peptidase-4, which increases stability and decreases immunogenicity and cytotoxicity. Its big size also slows absorption and lowers renal clearance. Because of these engineering characteristics, the formulation is soluble and has a longer half-life of approximately five days, which makes it appropriate for once-weekly subcutaneous injection [16]. Dulaglutide is licensed in various countries as an addition to diet and exercise for the treatment of individuals with type 2 diabetes [18]. In the clinical trial, once-weekly subcutaneous dulaglutide was an effective and generally well-tolerated treatment for adults with poorly controlled type 2 diabetes (T2D), including high-risk patients (e.g., obese and elderly patients, those with stage 3 or 4 chronic kidney disease (CKD) and/or cardiovascular (CV) disease) [19]. Dulaglutide was usually well accepted, with a minimal inherent risk of hypoglycemia. The most often adverse events in clinical studies were gastrointestinal-related, e.g., nausea, vomiting, and diarrhea [18]. Secondly, categories are gestational diabetes, a condition in which women who have not previously had diabetes encounter increased blood glucose levels during pregnancy, which has the potential to contribute to the development of type 2 diabetes [20]. There kinds of diabetes mellitus, including congenital diabetes, which is linked to genetic abnormalities of insulin production, cystic fibrosis-related diabetes, and steroid diabetes generated by high doses of glucocorticoids [21].

Using of animal model in the experiment

A crucial component of medical research is the use of animals, especially for assessing the efficacy and safety of novel medications prior to human trials. These medications are frequently tested in animal models during this preclinical phase [22]. Animal research is frequently thought to have limited application to humans due to the biological discrepancies between species and the diverse outcomes found in different animal models [23]. Animal models have been applied in scientific investigations to boost our comprehension and aid in the resolution of biological and biomedical inquiries [35]. The roots of our basic understanding of disease pathophysiology and human anatomy can mainly be traced to preclinical experiments employing numerous animal models [25]. One of the most potent techniques to produce experimental diabetes mellitus is chemical induction by Alloxan [26]. This chemical is widely recognized as a diabetogenic drug, extensively exploited in laboratory settings to produce both Type I and Type 2 diabetes in experimental animals [27]. A urea derivative called alloxan selectively necrotizes the pancreatic islets' β-cells [28]. Additionally, alloxan has been widely used to cause experimental diabetes in a variety of animal species, such as rabbits, rats, mice, and dogs, with different degrees of disease severity attained by altering the quantity of alloxan given [29]. Hence, it is used to induce diabetes in research animals. Alloxan's harmful effects on the pancreatic beta cells include the oxidation of important sulphydryl (SH) groups, inhibition of the formation of the glucokinase enzyme, generation of free radicals, and disturbance of intracellular calcium levels [30, 31]. Alloxan elicits a multifaceted reaction in the blood glucose level when administered to a test subject, causing a series of distinct phases corresponding inversely, alterations in the plasma insulin levels are observed, along with successive ultrastructural transformations in beta cells, culminating in their eventual necrotic demise [32]. Phases of alloxan activity (Phases 1). The first discernible stage in the first few minutes after alloxan injection is a brief drop in blood sugar levels that lasts for up to 30 minutes [33]. This small hypoglycemic response has been found to be the result of a brief stimulation of insulin secretion that was validated by an elevation of the plasma insulin concentration [33]. Phase 2: an increase in blood glucose levels that lasts for two to four hours characterizes the second stage, which starts an hour after alloxan administration. Furthermore, it has been noted that when the quantity of glucose rises, the amount of

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insulin in the blood also falls [34]. Phase three: the third stage of this phase is followed by a hypoglycemia phase that lasts for many hours and happens 4–8 hours later. This phase involves a large spike in insulin levels due to alloxan-induced rupture of secretory granules and cell membranes, leading to a marked period of transitional hypoglycemia in the bloodstream [35, 36]. These modifications are permanent and extremely indicative of a necrotic cell death of pancreatic islets [37]. Phase 4: the last and the 4th phase of the blood glucose response is the final permanent diabetic hyperglycemic phase during which complete degranulation and loss of the integrity of the beta cells within 24-48 h after administration of the alloxan takes place [38].

Effect of dulaglutide on HBA1C and vitamin B12 parameters

a) Effect on HbA1C

Dulaglutide monotherapy was considerably more effective than oral metformin monotherapy in improving glycemic control at 26 weeks. Although body weight was somewhat affected by both dulaglutide dosages (0.75 mg and 1.5 mg), only the higher dose showed a consistent and discernible decrease from baseline. Glycemic control and body weight were maintained with long-term treatment (up to 2 years) [39]. Patients with higher baseline HbA1c (<8.5%, ≥8.5%) concentrations were more likely to have favorable clinical responses to Dulaglutide [40]. Patients were sequentially randomized to once-weekly dulaglutide 1.5mg, 3.0mg, or 4.5mg for 52 weeks. Determining if dulaglutide 3.0 mg and/or 4.5 mg was superior to 1.5 mg in lowering HbA1c at 36 weeks was the main goal [41].

b) Effect on vit B12

Glucagon-like peptide-1 receptor agonists significantly altered the area of T2DM management by providing glycemic control in concert with weight loss. Nevertheless, FDA-approved GLP-1 receptor agonists frequently cause nausea, vomiting, and undesirable anorexia in certain thin T2DM patients. Crucially, the activation of central GLP-1 receptors is responsible for the hypo-phagic and emetic actions of GLP-1 receptor agonists. The development of dual agonists of GLP-1 receptors with glucose-dependent insulinotropic polypeptide (GIP) and conjugation with vitamin B12 or related corrin ring-containing compounds (corrination) are two distinct strategies to reduce the frequency and intensity of nausea and emesis associated with GLP-1 receptor agonists. Such techniques could lead to the creation of GLP-1 receptor agonists with higher therapeutic efficacy, thus minimizing treatment attrition, enhancing patient compliance, and extending treatment to a broader group of T2DM patients [42].

Materials and Methods

Study design

Experimental, randomized controlled animal study investigating the effects of Dulaglutide on glycemic control and vitamin B12 levels in alloxan-induced diabetic albino mice.

Animals

24 albino mice were obtained from the animal house at the University of Benghazi. They were chosen according to their weight and range from 20 to 30 g. The weight was measured by a triple-beam balance scale. Then, mice entered a sixty-day experimental period. The animal was housed in standard cages, maintained under controlled room temperature and humidity with a light and dark cycle. Divided into three cages, every cage contains 8 mice and a bottle of water.

Materials

In the current study experiment, mixed compositions were used to feed mice. This composition for a high-fat diet (HFD) is casein (BDH Chemicals Ltd., Poole, England). Cholesterol was purchased from NF-PH. FrancDL-methionine (LobaChemie), the vitamin and mineral mixture (ValupakMultivitamin), and yeast powder were procured from commercial sources. The mice were fed on HFD for two weeks. All these contents were crushed, mixed, kept in the fridge, and given daily for two weeks; each group received 5gm. All groups received a high-fat diet except the control group, which received a normal pellet diet (NPD) until the end of the experimental program. Weight was measured at the beginning, after one week, and after two weeks at the end of HFD. After two weeks, we noted an increase in the mice's weight.

Development of HFD-fed and alloxan–treated type 2 diabetic mice

The mice were distributed into a dietary regimen consisting of 24 mice by feeding either NPD or HFD (58% fat, 25% proteins, and 17% carbohydrate) as a proportion of total Kcal. After 2 weeks of dietary modification, a single dosage of alloxan 300 mg/kg dissolved with normal saline was given subcutaneously to induce diabetes in groups 2 and 3, except for group 1, which is the control group and received normal saline subcutaneously. After four hours of alloxan injection, change the water to dextrose because in this period, mice inter hypoglycemia due to the influence of enter the effect alloxan, after the effect. After 10 hours. After, replace the dextrose the dextrose to normal water to avoid hyperglycemia, also because of the action of alloxan. The number of mice dropped due to the toxicity of alloxan. After one week of alloxan injection, measure blood sugar in all groups. If blood sugar is more than 140 mg/dl, it will be considered diabetes.

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The Accu-Chek glucometer is used to measure blood sugar. Subsequently, group 3 (the testing group) received the therapy dulaglutide. Group one (control group) had NPD till the end of the experiment. Group 2HFD: the third group, mice were treated with subcutaneous (SC) dulaglutide from the local market at a dose of 0.75 mg/dl (single dose per week) for one month, administered by a tuberculosis (TB) syringe. Each cage contained four mice at the conclusion of the experiment. The experimental animals were sacrificed, and biochemical analyses were performed on the experimental mice's blood using the proper methods. To be checked for blood sugar, HbA1c, and vitamin B12 levels were investigated. HbA1c was measured by TOSOH G8, whereas Vit. B12 was measured by Cobas 411.

Statistical Analysis

Data were provided as means ± standard error of the mean (S.E.M.) of at least three independent studies. SPSS 24 software was used to analyze the data for statistically significant differences. Comparisons of two groups of data were done using Student's unpaired t-test. One-way ANOVA with post-hoc Dunnett's Comparison or Bonferroni's various comparison tests were employed to compare various groups of data. A probability level of 0.05 or smaller was judged statistically significant.

Results

HBA1C in Dulaglutide-treated mice compared to controls

(Table 1) shows that HbA1c levels were slightly higher in the positive control group compared to the dulaglutide-treated and negative control groups. However, the differences among the groups were not statistically significant, as indicated by the ANOVA p-value (p = 0.501). This suggests that dulaglutide treatment did not produce a significant reduction in HbA1c levels compared to untreated diabetic mice within the study period.

Table 1. Comparison between HbA1C levels among Dulaglutide-treated mice and controls (data are expressed as mean ±SEM)

Group	Mean (HbA1C)	Std. Error	ANOVA (p-value)
Negative control	4.5975	0.30535	0.501
Positive control	5.195	0.30910	
Dulaglutide-treated mice	4.8075	0.42386	
Total	4.8667	0.19764	

Significant value at the P< 0.05 level.

Vit. B12 in Dulaglutide-treated mice compared to control

On the other hand, (Table 2) demonstrates that vitamin B12 levels were noticeably lower in the positive control group compared to both the negative control and dulaglutide-treated groups, which showed similar values. Despite this trend, the difference among the groups was not statistically significant (p = 0.375), indicating that dulaglutide did not significantly influence vitamin B12 levels in diabetic mice under the conditions of this study.

Table 2. Comparison between Vit B12 levels among Dulaglutide-treated mice and controls (data are expressed as mean ±SEM)

Group	Mean	Std. Error	ANOVA (p-value)
Negative control	2000		0.375
Positive control	1699	287.37751	
Dulaglutide treated	2000		
Total	1899.6667	96.63398	

Comparison of the results included in both tables shows that neither HbA1c nor vitamin B12 levels demonstrated statistically significant differences between the dulaglutide-treated mice and the control groups. In (Table 1), HbA1c levels were slightly lower in the dulaglutide group compared to the positive control, indicating a modest improvement in glycemic control, but this was not significant. Similarly, (Table 2) shows that vitamin B12 levels were preserved in the dulaglutide group, unlike the reduction seen in the positive control group, yet the variation did not reach statistical significance (Figure 1. A and B). Overall, dulaglutide showed a trend toward better metabolic outcomes but without significant effects within the study period.

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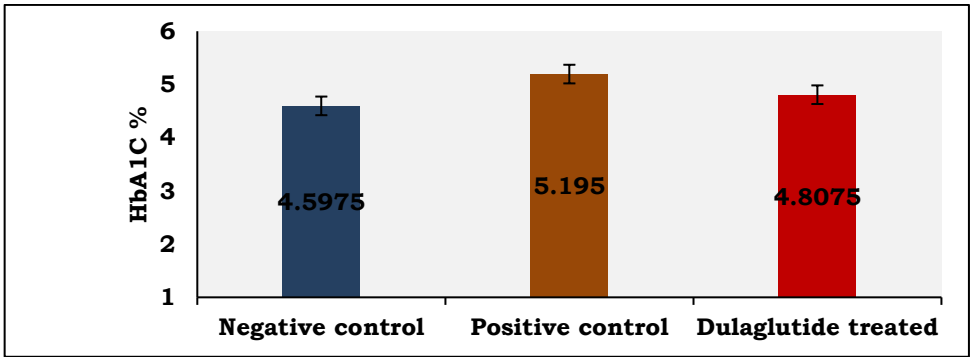
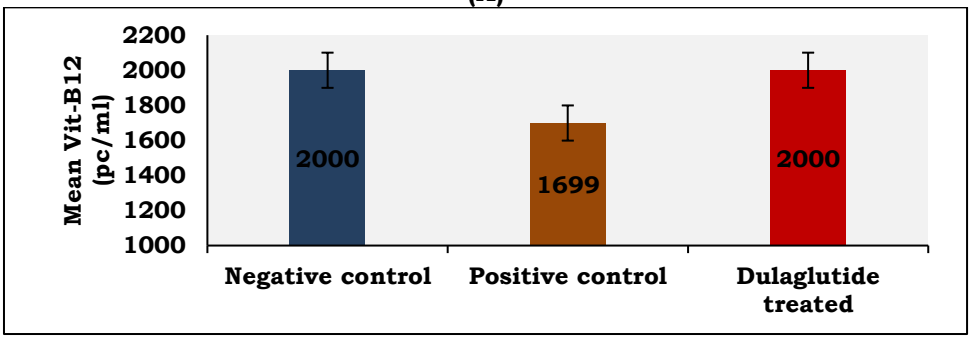


(A)



(B)

Figure 1. Comparison between (A) HbA1C and (B) Vit B12 levels among Dulaglutide-treated mice and controls (data are expressed as mean ± SEM)

Discussion

In this short-term alloxan-induced mouse study, dulaglutide produced a significant reduction in body weight but did not produce a significant change in HbA1c or vitamin B12 compared with controls. The observed weight loss is consistent with the well-documented, dose-dependent weight-reducing effects of dulaglutide and other GLP-1 receptor agonists in clinical trials and real-world cohorts. Large randomized trials have shown greater weight loss with higher dulaglutide doses (3.0–4.5 mg versus 1.5 mg) and consistent weight reduction across patient subgroups [55- 58]. The physiological mechanisms involved in high-fat diet-induced obesity are overconsumption of high-fat diets due to their low satiating effects, the high efficiency of dietary fat in being stored in the body, and the alterations in the hormones involved in energy balance, such as high-fat diet-induced hyperleptinemia and hyperinsulinemia, accompanied by leptin and insulin resistance [56].

The lack of a statistically significant reduction in HbA1c in your study is likely explained by several methodological and biological factors. First, clinical and real-world evidence indicate that meaningful, sustained HbA1c reductions with once-weekly dulaglutide typically emerge after months of therapy (commonly detectable at 3–6 months and persisting with longer follow-up). Short treatment duration (1 month) therefore reduces the probability of observing a significant glycated-hemoglobin change [59, 60]. A study employing a common electronic medical record system was carried out at five diabetic facilities in the Milan metropolitan area between 2016 and 2018. In a group of actual T2DM patients with inadequate glycemic control, the GLP-1 RA dulaglutide, given once a week at 1.5 mg, was successful in lowering HbA1c and reaching the goal level of 7.0%. The favorable effect on HbA1c was substantial after 6 months of treatment, remained for 12 months, was related to the reduction of body weight, and was independent of patients' age and sex. While patients with high HbA1c at baseline had the highest reduction of it at 6 and 12 months, low baseline [60]. Second, the alloxan model causes rapid β-cell destruction and severe insulin deficiency that may not mirror the insulin-resistant, β-cell–dysfunctional state of human T2D in which GLP-1 RAs act; this can blunt drug responsiveness and change the time course of biochemical recovery. Additionally, high early mortality and small group sizes reduce statistical power to detect moderate effects [61-64]. Similarly, retrospective research was undertaken in 120 individuals with T2DM who had commenced dulaglutide as an add-on to insulin therapy between January 2017 and December 2018. The change in glycated hemoglobin (HbA1c) was assessed following six months of treatment. Dulaglutide medication in combination with insulin resulted in a significant improvement in HbA1c and body weight over a 6-month period in a real-world clinical environment. Higher baseline HbA1c was related to a positive clinical response [64].

Vitamin B12 levels were unchanged after one month of dulaglutide in your mice. Current evidence does not support a direct, rapid effect of GLP-1 RAs on systemic B12 levels; reported nutritional deficiencies with GLP-1 RA therapy in humans are more commonly linked to prolonged anorexia, reduced intake, or concurrent medications (notably long-term metformin) rather than a direct pharmacologic depletion.

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Metformin is strongly associated with reduced B12 over months–years via altered intestinal absorption; thus, B12 alterations attributable to dulaglutide alone would be unexpected after only one month [65-67]. Key limitations are the short treatment duration (1 month), small sample size, alloxan model's abrupt β-cell loss, and high mortality, which together limit translational inference. Future preclinical work should use larger groups, longer treatment (≥3–6 months or longer depending on endpoints), consider partial β-cell dysfunction models (high-fat diet ± low-dose alloxan) to better mimic T2D, and include serial measures (body weight, fasting glucose, HbA1c at multiple timepoints) and nutritional intake monitoring. Monitoring B12 over longer periods and controlling for co-medications (e.g., metformin) will clarify whether GLP-1 RAs influence B12 status indirectly [68].

Conclusion

In this experimental study, dulaglutide showed a significant reduction in body weight in alloxan-induced diabetic mice but did not produce significant changes in HbA1c or vitamin B12 levels over the short treatment duration. These findings suggest that while dulaglutide may contribute to early weight improvement, longer treatment periods and larger sample sizes are needed to fully evaluate its therapeutic effects on glycemic control and vitamin B12 status. Further studies using models that better mimic type 2 diabetes progression are recommended to clarify the long-term metabolic benefits of dulaglutide.

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Conflicts of Interest

The authors declare no conflicts of interest.

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