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Therapeutic Potential of Sunitinib in Ameliorating Endothelial Dysfunction in Type 2 Diabetic Rats

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Keywords
Sunitinib · Endothelial function · Diabetes · Glucose · Microcirculation

Abstract
Introduction: Sunitinib, a multi-targeted tyrosine kinase receptor inhibitor used to treat renal-cell carcinoma and gastrointestinal stromal tumor, was recently shown to have a beneficial effect on metabolism in type 2 diabetes (T2D). Endothelial dysfunction is a key factor behind macro- and microvascular complications in T2D. The effect of sunitinib on endothelial function in T2D remains, however, unclear. We therefore tested the hypothesis that sunitinib ameliorates endothelial dysfunction in T2D. ***Methods:*** Sunitinib (2 mg/kg/day, by gavage) was administered to T2D Goto-Kakizaki (GK) rats for 6 weeks, while water was given to GK and Wistar rats as controls. Hemodynamic, inflammatory, and metabolic parameters as well as endothelial function were measured. ***Results:*** Systolic, mean arterial blood pressures, plasma tumor necrosis factor α levels, kidney weight to body weight (BW) ratio, and glucose levels were higher, while BW was lower in GK rats than in Wistar rats. Six-week treatment with sunitinib in GK rats did not affect these parameters but suppressed the increase in glucose levels. Endothelium-dependent relaxations were reduced in both aortas and mesenteric arteries isolated from GK as compared to Wistar rats, which was markedly reversed in both types of arteries from GK rats treated with sunitinib. ***Conclusions:*** This study demonstrates that sunitinib has a glucose-lowering effect and ameliorates endothelial dysfunction in both conduit and resistance arteries of GK rats.

Introduction

Type 2 diabetes (T2D) is an important risk factor for the development of cardiovascular diseases, including atherosclerosis and ischemic heart disease [1]. Both mac-

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rovascular and microvascular complications significantly contribute to the increase in mortality and morbidity in the large group of patients with T2D [1]. Endothelial dysfunction represents an early hallmark for cardiovascular complications in patients with T2D and plays a pivotal role in the etiology of T2D-induced vascular complications. The underlying disease mechanisms for the development of endothelial dysfunction in T2D are complex, but important components are decreased bioavailability of nitric oxide and increased formation of reactive oxygen species [2, 3]. The outcomes of clinical trials evaluating the effect of intensive glycemic control using established hypoglycemic agents, such as metformin and insulin, have not convincingly demonstrated overall beneficial effects on cardiovascular events [4]. New drug targets such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitor have been shown to exert beneficial effects on cardiovascular outcomes through glucose-independent mechanisms [5]. There is still a clinical need for improved understanding of the underlying disease mechanism in order to develop new therapeutic strategies for the treatment of vascular complications in T2D.

Sunitinib is an orally available tyrosine kinase inhibitor and the first-line therapy for treating metastatic renal-cell carcinoma [6]. Sunitinib exerts its therapeutic effect via inhibition of several members of the split-kinase domain family of receptor tyrosine kinase including vascular endothelial growth factor receptor (VEGFR) 2 [6]. Despite side effects of hypertension and cardiac toxicity in cancer patients treated with sunitinib [7], emerging studies have shown a beneficial effect of sunitinib on overall metabolism in T2D [8]. Case reports have indicated that sunitinib treatment resulted in hypoglycemia in a non-diabetic patient [9] and improvement in glycemic control and need for less intensive glucose-lowering treatment in a patient with T2D [10]. Experimental studies demonstrated that sunitinib could prevent β-cell apoptosis and hemorrhage in the microcirculation of pancreatic islets, decrease glucose levels, and improve insulin sensitivity in spontaneously T2D rats [11]. Whether sunitinib also exerts beneficial effect on T2D-associated vascular complications remains unclear.

Consequently, we aimed to study the therapeutic potential of sunitinib for the treatment of endothelial dysfunction in T2D. Using Goto-Kakizaki (GK) rats, an established model of T2D that exhibits metabolic derangement and vascular dysfunction [3, 12, 13], we evaluated the effect of chronic sunitinib treatment on endothelial function in both conduit and resistance arteries.

Materials and Methods

Drugs and Solutions

Acetylcholine (ACh) and sodium nitroprusside (SNP) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sunitinib-L-malate (sunitinib) was obtained from patients who discontinued treatment at Erasmus University Medical Center, Rotterdam, The Netherlands [14]. All drugs were obtained with distilled water.

Animals and Sunitinib Treatment

All experimental protocols were performed in accordance with the Guide for Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1996) and approved by the regional Ethical Committee for animal experiments in Stockholm (17708-2019). Male Wistar rats were purchased from Charles River (Sulzfeld, Germany) and housed in the animal facility of Karolinska University Hospital (L5) and Karolinska Institutet (comparative medicine). GK rats were derived from glucose-intolerant Wistar rats and were bred in the animal facility. The GK strain was established from normoglycemic Wistar rats by repeated inbreeding in each successive generation of the siblings with the highest blood glucose levels during an oral glucose tolerance test [12]. All animals were kept at 22°C, with 12-h light/dark cycle and free access to standard chow and water. Wistar rats were treated with water and age- and sex-matched GK rats were treated with water or sunitinib (2 mg/kg/day, by gavage) at the age of 10–15 weeks for 6 weeks. Body weight (BW), blood pressure (BP), and blood glucose were monitored before and at the end of the treatment. After the chronic treatment, animals were anesthetized with pentobarbital (50 mg/kg, i.p.) followed by collection of different organs and plasma. Wet kidney weight was measured, aortas and mesenteric arteries (MAs) were dissected for the evaluation of vascular function in the wire myograph, and insulin and tumor necrosis factor (TNF) α were measured (see below).

Hemodynamic Measurement

Rats were anesthetized with pentobarbital (50 mg/kg, i.p.). Right carotid artery was cannulated with a PE-50 catheter which was connected to a pressure transducer for BP registration. The animal was then tracheotomized and intubated to ventilate lungs with room air during the experiment. Arterial pressure was recorded with PharmLab V5.0 (AstraZeneca R&D, Mölndal, Sweden).

Immunoassay

Plasma levels of TNFα and insulin were measured using ELISA (ThermoFisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions.

Tissue Preparation and Wire Myograph Study

Rat thoracic aortas and MAs (the third-order branch) were cleaned by removing fat and connective tissues under microscope and subsequently cut transversely into 2-mm rings. The vessels were then mounted on a wire myograph (Danish Myo Technology) in separate organ baths containing 6 mL Krebs-Henseleit (KH) buffer. The KH buffer (pH 7.4) containing (in mM) 118 NaCl, 4.7 KCl, 1.2 $MgSO_4$, 1.2 KH_2PO_2, 25 $NaHCO_3$, 11 glucose, and 2.4 $CaCl_2$ was maintained at 37°C and aerated with 95% O_2/5% CO_2.

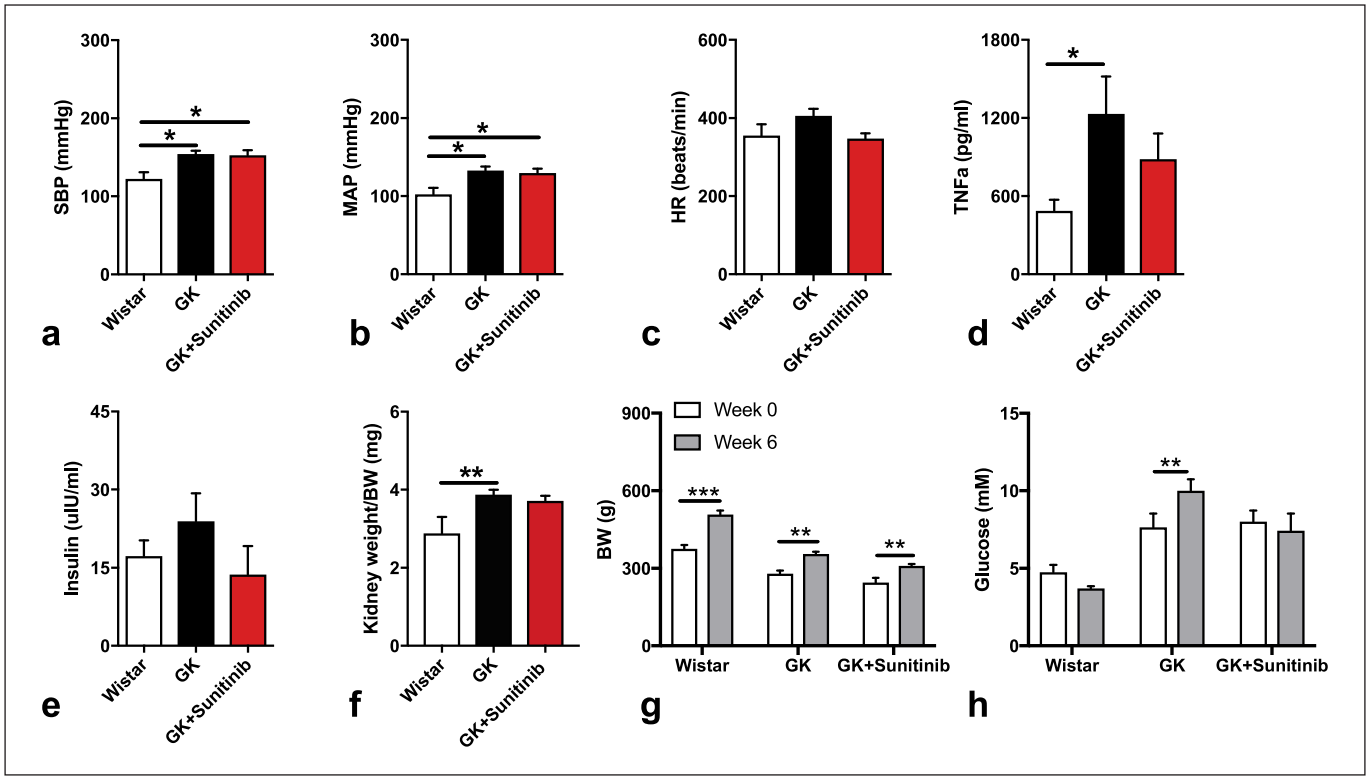

Fig. 1. Hemodynamic, inflammatory, and metabolic changes induced by sunitinib. Effect of sunitinib on SBP (**a**, $n = 4$), MAP (**b**, $n = 4$), HR (**c**, $n = 4$), plasma TNFα levels (**d**, $n = 7–13$), plasma insulin levels (**e**, $n = 6–12$), and kidney-to-BW ratio (**f**, $n = 6–11$). Measurement of BW (**g**) and blood glucose (**h**) at baseline and following 6-weeks sunitinib treatment in rats from 3 groups ($n = 4–10$): Wistar rats, nontreated GK rats, and sunitinib-treated GK rats (GK + sunitinib). Week 0: treatment week 0; week 6: the end of treatment week 6. Data are presented as means ± SEM. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. GK, Goto-Kakizaki; TNF, tumor necrosis factor; SBP, systolic blood pressure; MAP, mean arterial hypertension; HR, heart rate; BW, body weight.

Changes in contractile forces were recorded with a Harvard isometric transducer. The vessel rings were exposed to KCl twice (50 mM and 100 mM, respectively for aortas; 50 mM each time for MAs) to check the contractility. Thereafter, vessels were allowed to equilibrate in fresh KH buffer for 30 min. Endothelium-dependent relaxation (EDR) was determined in phenylephrine (PE, 1 μM)-preconstricted vessels by administration of ACh (10^{-9}–10^{-5} M). Endothelium-independent relaxation was evaluated with 10 μM SNP [3].

Statistical Analysis

Vascular relaxation to ACh or SNP was expressed as the percentage of contraction to PE. One-way ANOVA with post hoc Bonferroni's test or Kruskal-Wallis one-way ANOVA was used to compare multiple groups. A paired or unpaired *t* test was used for comparison between 2 groups. Concentration responses were assessed using two-way ANOVA followed by post hoc Bonferroni's test. All data are represented as means ± SEM. Two-sided $p < 0.05$ was considered as statistically significant. Analyses were carried out with GraphPad Prism v.7 ©.

Results

Hemodynamics, Inflammatory, and Metabolic Changes Induced by Sunitinib

In accordance with previous studies [15, 16], the systolic BP and mean arterial pressure were significantly higher in GK than in Wistar rats (Fig. 1a, b). Sunitinib had no effect on systolic BP, mean arterial pressure, and heart rate (Fig. 1a–c). Plasma TNFα levels were significantly higher in GK rats versus Wistar rats, which was not affected by sunitinib treatment (Fig. 1d). Plasma insulin levels were not significantly different among Wistar, GK, and GK + sunitinib groups; despite that, there was a trend for higher levels in the GK versus Wistar group (Fig. 1e). The kidney-to-BW ratio was higher in GK rats versus Wistar rats but was not affected by sunitinib treatment in GK rats (Fig. 1f). In line with previous studies [3, 17], BW was lower in age-matched GK rats versus Wistar rats (g:

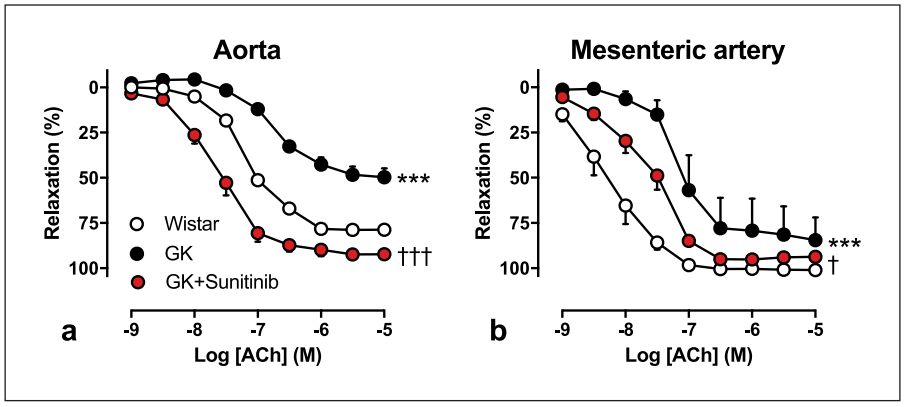

Fig. 2. Effect of the 6-week treatment with sunitinib (2 mg/kg/day) on endothelial function in T2D. EDR in response to increasing concentrations of ACh in aortic rings (**a**, n = 6–9) and MAs (**b**, n = 4–9) preconstricted with PE isolated from Wistar, GK, and GK + sunitinib groups. Data are presented as means ± SEM. ***$p < 0.001$ versus Wistar, $^{\dagger}p < 0.05$, $^{\dagger\dagger\dagger}p < 0.001$ versus GK. T2D, type 2 diabetes; ACh, acetylcholine; EDR, endothelium-dependent relaxation; PE, phenylephrine; MAs, mesenteric arteries; GK, Goto-Kakizaki.

Table 1. KCl-, PE-, and ACh-mediated vascular function in aortas and MA

Vascular function, aorta/MA	Wistar	GK	GK + sunitinib
KCl contraction (ΔmN)	11.0±0.9/3.5±1.2	9.9±1.0/5.7±1.2	10.5±0.9/4.6±0.8
PE contraction (ΔmN)	11.6±1.8/5.7±1.7	10.2±1.5/10.1±2.2	8.9±0.5/4.6±0.8
ACh relaxation (-logEC50)	7.2±0.05/8.3±0.12	6.7±0.09/7.2±0.22	7.7±0.07/7.6±0.08

Values are means ± SEM. No significant differences were detected for KCl and PE using Kruskal-Wallis one-way ANOVA. ACh, acetylcholine; MAs, mesenteric arteries; PE, phenylephrine; GK, Goto-Kakizaki.

375 ± 1.7 in Wistar vs. 279 ± 0.4 in GK rats; $p < 0.01$). The increases in BW during 6 weeks in GK rats were not affected by sunitinib treatment (Fig. 1g). Glucose levels were higher in GK rats versus Wistar rats at baseline (mM: 4.7 ± 0.2 in Wistar vs. 7.7 ± 0.2 in GK rats; $p < 0.05$). Glucose levels were significantly increased over time in GK compared to Wistar rats (Fig. 1h). Of note, no increase in glucose levels was observed in GK rats treated with sunitinib (Fig. 1h). These observations indicate that sunitinib inhibited the increase in glucose levels over time but did not affect hemodynamics or inflammatory parameters in GK rats.

Effect of Sunitinib Treatment on Endothelial Function in GK Rats

The PE- and KCl-induced contraction in aortas and MAs did not differ significantly among Wistar, GK, and GK + sunitinib groups (Table 1). In accordance with previous studies [3, 18], endothelial dysfunction was present in GK rats as reflected by an impaired EDR in both aortas and MAs (Table 1; Fig. 2a, b). Following the 6-week sunitinib treatment in GK rats, EDR was markedly improved both in conduit aortas and in resistance MAs (Table 1; Fig. 2a, b). The SNP single concentration-induced endothelium-independent relaxation in these arteries was not affected by sunitinib (GK aorta: 97 ± 1.3% vs. GK aorta+sunitinib: 99 ± 0.2%; GK mesenteric: 99 ± 0.9% vs. GK mesenteric+sunitinib: 98 ± 1.8%). These findings indicate that chronic treatment with sunitinib ameliorates endothelial dysfunction in both conduit and resistance arteries in GK rats.

Discussion

To the best of our knowledge, this is the first study evaluating the potential therapeutic effect of sunitinib on endothelial function as an endpoint in T2D. The main findings are that chronic treatment with sunitinib had glucose-lowering effect in GK rats and markedly ameliorated endothelial dysfunction in both conduit aortas and resistance MAs isolated from GK rats (Fig. 3). These results suggest that sunitinib exerts beneficial vascular and glucometabolic effects in T2D with potentially important implications which are discussed below.

Sunitinib is the first-line strategy for treating metastatic renal-cell carcinoma via inhibition of receptor tyrosine kinase including VEGFR2 [6]. Several lines of evidence

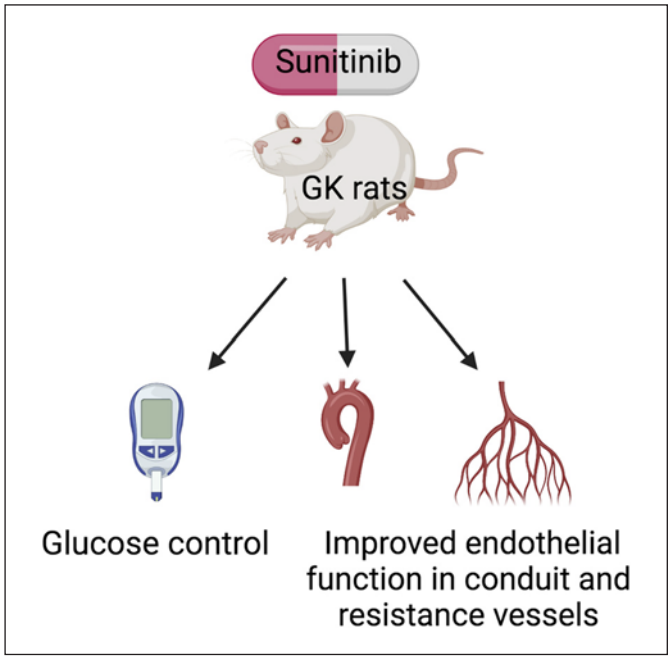

Fig. 3. Schematic summary of the study. Chronic treatment with sunitinib in type 2 diabetic GK rats significantly improves the glucose control and attenuates endothelial dysfunction in both conduit aortas and resistant MAs. GK, Goto-Kakizaki; MAs, mesenteric arteries (generated with BioRender under license).

suggest that sunitinib may have favorable effects on the diabetic metabolism. In a case report, it was described that a patient with T2D experienced improvement in glycemic control and less intensive anti-glycemic treatment following sunitinib treatment [10]. Sunitinib prevented β-cell apoptosis and hemorrhage in the microcirculation of pancreatic islets, decreased glucose levels, and improved insulin sensitivity in spontaneously T2D rats [11]. Of interest, a single intravitreous injection of sunitinib microparticles in an animal model was recently shown to suppress choroidal neovascularization for 6 months and to block VEGFR-mediated leukostasis and retinal nonperfusion, which are associated with diabetic retinopathy progression [19]. This suggests that sunitinib has potential to be beneficial in the treatment of diabetes-induced vascular complications. Based on the fact that endothelial dysfunction plays a pivotal role in the etiology of T2D-induced vascular complications, we set out to investigate the therapeutic potential of sunitinib in attenuating endothelial dysfunction in T2D. We found that chronic treatment with sunitinib not only had glucose-lowering effect in GK rats but also attenuated endothelial dysfunction in both conduit aortas and resistance MAs. These observations support the concept that sunitinib has the potential to be beneficial in the treatment of diabetes-induced vascular complications. The beneficial effect of sunitinib on endothelial function in GK rats may be associated with the glucose-lowering effect, which can lead to increase in nitric oxide bioavailability and decrease in reactive oxygen species formation [20, 21]. It is also likely that the improvement is in part attributed to the direct effect of sunitinib on the endothelium as sunitinib treatment or inhibition of the VEGFA-VEGFR2 pathway prevented aneurysm formation and progression in mice [22]. However, such benefits are unlikely to be associated with attenuation of inflammatory and insulin signaling pathways as sunitinib had no significant effects on inflammatory marker TNFα and insulin levels. The exact mechanisms underlying attenuation of endothelial dysfunction by sunitinib are not readily known and warrant further investigations.

It is important to note that treatment with sunitinib can induce hypertension in both clinical and experimental studies, which is known as a common side effect of cancer treatment [14, 23–26]. The mechanistic insights underlying the rise in BP in both humans and animals have pointed to the involvement of endothelin [14, 23, 27]. This seems to rely on different dosages of sunitinib applied [8]. The dose of sunitinib (2 mg/kg) used in the present study is comparable to those (1.5–2.5 mg/kg) used in experimental studies reporting the beneficial effect for diabetes, although the side effects were not checked but is lower than those used in studies demonstrating hypertensive effect and upregulation of the endothelin system (7–26.7 mg/kg) [11, 25]. In the present study, sunitinib treatment did not further increase BP of GK rats whose BP was already high as compared to Wistar rats at the basal condition. This is also reflected by the lack of effect on the heart rate in GK rats following sunitinib treatment. The already high BP at baseline in GK rats may mask the side effect by sunitinib. It should also be noted that the sunitinib-induced hypertension may also affect endothelial function depending on the dose of sunitinib. Thus, endothelial dysfunction was observed in rats treated with a high dose of sunitinib (26.7 mg/kg) [14], while endothelial function was preserved in rats with 14 mg/kg sunitinib [28]. This should be compared to the dose of 2 mg/kg in the present study resulting in improved endothelial function in T2D. Thus, a low dose seems to exert beneficial vascular effects with no negative side effect on BP.

Some limitations are worth mentioning. First, endothelial function was evaluated ex vivo, which does not ful-

ly reflect the in vivo situation. Sunitinib may exert effects on multiple systems in vivo to influence endothelial function in T2D. The effect of sunitinib on other vascular aspects, for example, vascular remodeling warrants further investigations. Moreover, the dose of sunitinib (2 mg/kg) used in the present study is similar to those used in experimental studies reporting the beneficial effect for diabetes, although side effects were not checked (1.5–2.5 mg/kg) but is lower than those used in studies demonstrating a hypertensive effect and upregulation of the endothelin system (7–26.7 mg/kg) [11, 25]. However, this dosage was only applied to GK rats. The optimal dose of sunitinib needs to be tested in both T2D and healthy groups to control for the side effect and to achieve the maximal therapeutic effect for the favorable vascular effects in T2D.

In conclusion, the present study demonstrates that chronic treatment with sunitinib improves glucose control and ameliorates endothelial dysfunction in both conduit and resistance arteries of T2D rats without major cardiovascular side effects. This may pave the way for additional endpoints in the future trials, evaluating the clinical efficacy of sunitinib.

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Statement of Ethics

This study was conducted in accordance with the Guide for Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1996) and approved by the regional Ethical Committee for animal experiments in Stockholm (17708-2019).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Z.Z. conceived and designed the study; A.M., T.J., Y.T., B.W., and Z.Z. performed and collected research data; A.M., T.J., and Z.Z. analyzed research data and performed statistical analyses; A.M., T.J., Y.T., B.W., J.Y., C.G.O., A.H.D., J.P., and Z.Z. contributed to discussion; A.M. and Z.Z. wrote the manuscript; A.M., T.J., J.P., and Z.Z. edited the manuscript; and all the authors reviewed the final version of the manuscript.

Data Availability Statement

All data generated or analyzed are included in this article. Further inquiries can be directed to the corresponding author.

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