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Ameliorative effect of selenium yeast in combination with pioglitazone on diabetes outcomes in streptozotocin-induced

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ABSTRACT

Anti-diabetic therapies possess many side effects; thus, searching for alternative strategies with low cost, minimal side effects, and high therapeutic value is very important. The present study aimed to explore the combined use of selenium yeast (SY) and standard anti-diabetic drug pioglitazone (PGZ) for diabetes

mellitus (DM) treatment in streptozotocin (STZ)-induced DM. STZ was injected daily intraperitoneally with a low dose (40 mg/kg) into Sprague-Dawley rats to induce DM. The synergistic effect of the SY (0.2 mg/kg) and PGZ (0.65 mg/kg) on DM complications was evaluated after 88 weeks of treatment. The impact of our medication on glucose levels, insulin sensitivity, lipid abnormalities, oxidative mediators, and inflammatory markers was assessed by biochemical techniques. STZ-induced diabetes has toxic effects, including toxic hepatic tissues, lipid disturbances, massive oxidative damage, and hyperinflammation. Experimental rats either treated with monotherapy alone or combined therapy resulted in a significant anti-diabetic effect. The PGZ+ SY combination has the best effect, as illustrated by significant ($P < 0.05$) decreases in fasting blood glucose, (FBG) insulin, HbA1c, and HOMA-IR levels. This combination attenuated ($P < 0.05$) lipid disturbances and their associated elevated atherogenicity biomarkers. At the same time, treatments with PGZ+ SY exhibited an anti-inflammatory effect as they ameliorated the increase in inflammatory parameters (CRP, TNF-α, IL-6). Also, it restored the total antioxidant capacity and peroxisome proliferator-activated receptor (PPARϒ) levels that were decreased by STZ-DM induction. In conclusion, this study finds PGZ+ SY as a promising DM therapeutic alternative. This synergistic combination alleviates most DM-related complications and insulin resistance.

Keywords: *Selenium yeast; Pioglitazone; Anti Pioglitazone; Anti-diabetic; Antioxidant; Anti Antioxidant; Anti-inflammatory*

INTRODUCTION

Diabetes mellitus (DM) is a metabolic syndrome caused by a relative or absolute insulin shortage that causes hyperglycemia and impairs the metabolism of lipids, proteins, and carbohydrates.[1] In 2017, DM global prevalence was reported as 451 million, projected to be 693 million by 2045.[2] Furthermore, during the previous two decades, the number of people diagnosed with Type 2 diabetes has more than doubled, particularly in developing nations.[3,4] The management of DM in modern conventional medicine is based on physical exercise, dietary measures, insulin therapy, and oral hypoglycemic drugs.[5,6] Current diabetes therapies include several negative side effects, including flatulence, diarrhea, indigestion, vomiting, nausea, renal failure, hypoglycemia, and others.[7] Moreover, long-standing DM patients produce serious complications related to the heart, blood vessels, nerves, kidneys, and eyes.[8] Thus, due to their low cost, minimal side effects, and therapeutic value, herbal treatments have gained much interest and popularity in recent years.[9]

Selenium (Se) is a nutritionally important trace element that regulates various biological protective systems in humans, including anti-oxidation, autophagy dysfunction improvement, anti-inflammation, anti-apoptosis, and anti-cancer.[10,11] Selenium is classified into elemental, inorganic, and organic forms.[12] In animals, inorganic and organic Se are two dietary forms.[13] In animal tissues, the organic Se has greater bioavailability, absorption, and more severe physiological and biochemical benefits than the inorganic form.[14] Se yeast (SY) is an enriched, recognized organic selenium source that is naturally present in various food types.[15] Although selenium's role

in chronic disease prevention is undoubted, much research on selenium evaluated its potential benefits as an anti-cancer and antioxidant agent.[11] Limited studies have reported the impact of SY administration on the attenuation of DM and its related complications.[15]

Peroxisome proliferator-activated receptors (PPARs) are essential in stimulating many biologic processes, including cell differentiation and growth, immune response, insulin sensitivity, adipogenesis, and lipid metabolism.[16] One ligand for PPAR-γ, one of thiazolidinediones (TZD), is pioglitazone (PGZ). It is an effective oral anti-hyperglycemic therapy that also has lipid and cardiovascular (CV) advantages, allowing T2DM patients to be successfully managed.[17]

The purpose of this study was to assess the anti-diabetic effects of SY alone and in combination with PGZ, including glucose-related parameters [blood glucose, glycosylated hemoglobin (HbA1c), insulin, homeostatic model assessment of insulin resistance (HOMA-IR), lipid profile, anti-inflammatory, and antioxidant activities].

MATERIAL AND METHODS

Ethical considerations

All animal research studies were approved by Jordan University's Animal Ethics Committee and were out by the National Research Council's guidelines for animal care and use.[18]

Reagents and materials

PGZ raw material (HCl powder, 98.5%; Lot # BWP200023) was obtained from Dar Al Dawa, Jordan. Streptozotocin (>95%; bioXTra, UK, Lot # 18883-66-4) and SY (ISURA Co., USA) were purchased. All enzyme immune assay kits [including interleukin (IL)-6 and tumor necrosis factor-α (TNF-α)] were purchased from MyBioSource, USA. The following instruments were used in the study: Multiskan Go Spectrophotometer, Model 1510, Thermo Fisher, UKBath, Sonicator Crest model-175T (UltraSonics CORP), Sartorius analytical balance, and Centrifuge (Eppendorf 5417C).

Animals, diabetic induction, and study design

Forty-five mature healthy male Sprague-Dawley rats (220–300 g) were obtained from Jordan University's Animal House, School of Graduate Studies. Under standardized environmental and nutritional necessities, all rats were housed with free access to food and water. Animals are classified into five main groups (nine rats in each group). G0 (Negative control) received CMC solution (buffer solution). All other groups were subsequently intraperitoneally given a low amount of streptozotocin (STZ) [40 mg/kg of freshly prepared STZ solution (32.25 mg/ml in 0.05 M sodium citrate buffer, pH 4.5)]. T2DM was obtained in animals when FBG was ≥120 mg/dL, and non-FBG was ≥250 mg/dL. G1 was baseline diabetic animals, G2 [PGZ (0.65 mg/kg) alone], G3 [SY (0.2 mg/kg) alone], and G4 [PGZ (0.65 mg/kg) and SY (0.2 mg/kg)]. Selenium and pioglitazone doses were administered orally and once daily using gastric gavage during the experimental weeks.

Evaluation of diabetic-related lipid profile, anti-inflammatory, and antioxidant parameters

Before, during, and after the treatment stage (about 6 weeks), cardiac punctures and blood were collected into plain tubes. HbA1c (Automatic protein analyzer, GenruiPA120) and FBG (SPINREACT, Spain) were analyzed using fresh blood. The remaining fresh blood was left to clot and then centrifuged to obtain serum. The specimens were preserved and frozen for biochemical testing. Selenium, leptin, PPAR-, insulin, TNF-IL-6, C-reactive protein (CRP), and total antioxidant capacity (TAC) (all from MyBioSource, Rat, ELISA Kits) and lipid profile (cholesterol, triglycerides, LDL-C, and HDL-C) (all from SPINREACT, Spain) were all measured using specialized kits and following the manufacturers' detailed instructions. HOMA-IR was computed

using the following formula: [fasting insulin (μ/mLL) × fasting glucose (mmol/L) / 22.5].[19]

Statistical analysis

The results are presented as mean ± standard error of the mean. $P < 0.05$ was judged statistically significant. A one-way analysis of variance (ANOVA) was used to analyze the data from different groups, followed by a Tukey–Kramer post hoc test. Pearson's correlation test was performed to evaluate the interrelationships between biomarkers. The data were analyzed using statistical software (SAS version 9, USA).

RESULTS

Weight change, food and water intake between untreated and treated rats

Due to damage to the pancreas, STZ injection resulted in the onset of DM. During the study course, body weight varied significantly ($P < 0.05$) as a function of diets. Also, feed intake increased significantly ($P < 0.05$) in the diabetic groups. Water intake increased significantly with the passage of the study compared to non-diabetic rats. With DM induction, liver weights significantly increased (G1), and this effect was attenuated in treatment groups, especially SY- (G3) and PGZ+ SY- (G4) treated groups (Table 1).

Effect of pioglitazone and selenium yeast on diabetic markers

After the trial, STZ-induced diabetic rats had severe hyperglycemia and substantially ($P < 0.05$) higher FBG, serum insulin, HbA1c, and HOMA-IR values than normal non-diabetic rats (G0). Although, both PGZ and SY therapies reduced these diabetes parameters, their combination had the most impact, with the PGZ+ SY treated group showing a substantial drop in FBG, serum insulin, HbA1c, and HOMA-IR levels when compared to the diabetic control group (G1) (Table 2).

Effect on lipid profile and atherogenic biomarkers

Table 3 displays the plasma levels of total cholesterol, triglycerides, LDL-C, and HDL-C in all the experimental groups of rats. When compared to the ordinary non-diabetic group (G0), the diabetic control (G1) group had a substantial rise in cholesterol, triglycerides, and LDL-C ($P < 0.05$). They were also

TABLE 1. Body weight, food and water intakes, and liver weight of the study groups.

Variables	Non-Diabetic Control	Streptozotocin-Induced Diabetic Groups			
		Control	PGZ	SY	PGZ + SY
	(n = 9)	(n = 9)	(n = 9)	(n = 9)	(n = 9)
Initial weight (g)	249 ± 14	231.6 ± 1.5	244.0 ± 7.8	274.0 ± 15.9	237.2 ± 4.2
Final weight (g)	253.1 ± 14.2	221.0 ± 2.2	227.3 ± 5.8	248.4 ± 13.2	222.2 ± 6.2
Δ Weight (g/day)	0.09 ± 0.01	−0.25 ± 0.03	−0.40 ± 0.07[a]	−0.61 ± 0.26[a]	−0.36 ± 0.11[a]
Food intake (g/day)	0.32 ± 0.01	0.50 ± 0.0	0.96 ± 0.02[a,b]	0.71 ± 0.01[a,c]	0.71 ± 0.01[a,c]
FER	27.58 ± 3.14	−0.5 ± 6.99[a]	−41.34 ± 7.8[a]	−85.6 ± 35.7[a]	−51.3 ± 15.5[a]
Water intake (mLL/day)	0.93 ± 0.01	1.85 ± 0.0[a]	2.89 ± 0.04[a,b]	2.60 ± 0.01[a,b]	2.34 ± 0.01[a,b]
Liver weight (g)	7.52 ± 0.24	8.77 ± 0.27[a]	8.01 ± 0.13	6.9 ± 0.13[b,c]	7.67 ± 0.14
Liver index	3.05 ± 0.20	3.97 ± 0.13[a]	3.54 ± 0.10	2.84 ± 0.15[b]	3.47 ± 0.07

Values are the means ± SEM. Abbreviations: PGZ: pioglitazone; SY: selenium-yeast; FER: food efficiency ratio (bodyweight change/100g food intake); liver index: liver weight (g)/100g final body weight. Values are significantly different at $P < 0.05$. [a]significantly different from non-diabetic control, [b]significantly different from diabetic control,[c] and significantly different from PGZ alone treated group.

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TABLE 2. Diabetic markers between untreated and treated rats.

Variables	Non-Diabetic Group	Streptozotocin-induced diabetic groups			
		Control	PGZ	SY	PGZ+ SY
	(n = 9)	(n = 9)	(n = 9)	(n = 9)	(n = 9)
FBG (mg/dL)	116 ± 1.0	347 ± 1.0[a]	240 ± 1.0[a]	329.1 ± 26.7[a]	214 ± 6.0[b]
HbA1C	3.39 ± 0.05	4.71 ± 0.05[a]	3.76 ± 0.02	4.54 ± 0.99	3.67 ± 0.15[b]
Insulin (mLUL/L)	12.84 ± 0.33	18.25 ± 0.18[a]	14.11 ± 0.02[b]	16.21 ± 0.26[a]	13.87 ± 1.55[b]
HOMA-IR	3.67 ± 0.07	15.65 ± 0.18[a]	8.37 ± 0.04[b]	13.18 ± 1.08[a]	7.37 ± 0.87[b]

Values are the means ± SEM. Abbreviations: PGZ: pioglitazone; SY: selenium-yeast; FBG: fasting blood glucose; HbA1C: glycosylated hemoglobin; HOMA-IR: homeostatic model assessment of insulin resistance. Values are significantly different at P< 0.05.significantly different from the non-diabetic control [b]and significantly different from diabetic control.

TABLE 3. Lipid and atherogenic biomarkers between untreated and treated rats.

Variables	Non-Diabetic Group	Streptozotocin-induced diabetic groups			
		Control	PGZ	SY	PGZ+ SY
	(n = 9)	(n = 9)	(n = 9)	(n = 9)	(n = 9)
Cholesterol (mg/dL)	54.9 ± 0.3	106.2 ± 1.0[a]	70.8 ± 0.9	89.3 ± 14.3	68.9 ± 4.1[b]
LDL-C (mg/dL)	20.88 ± 0.49	67.12 ± 0.8[a]	36.55 ± 1.05[a]	45.7 ± 5.4[a]	30.18 ± 1.66[b]
HDL-C (mg/dL)	27.62 ± 0.13	12.13 ± 0.3[a]	24.44 ± 0.41[b]	19.4 ± 1.56[a]	25.26 ± 1.97[b]
Triglycerides (mg/dL)	39.5 ± 1.1	134.8 ± 1.1[a]	86.8 ± 0.6[a]	131.9 ± 16.4[a]	78.8 ± 5.0[b]
LDL-C/HDL-C	0.76 ± 0.02	5.56 ± 0.15[a]	1.50 ± 0.05[b]	2.6 ± 0.44[a]	1.26 ± 0.13[b]
Cholesterol/Triglycerides	1.40 ± 0.04	0.79 ± 0.01[a]	0.82 ± 0.01[a]	0.80 ± 0.16[a]	0.90 ± 0.06
AIP	0.15 ± 0.01	1.05 ± 0.01[a]	0.55 ± 0.01[a,b]	0.81 ± 0.10[a]	0.50 ± 0.05[b]
CRR	1.99 ± 0.02	8.79 ± 0.19[a]	2.90 ± 0.06[b]	4.96 ± 0.97[a]	2.89 ± 0.32[b]
AC	0.99 ± 0.02	7.79 ± 0.19[a]	1.90 ± 0.06[b]	3.96 ± 0.97[a]	1.89 ± 0.32[b]

Values are the means ± SEM. Abbreviations: PGZ: pioglitazone; SY: selenium-yeast; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; AIP: atherogenic index of plasma [log (Triglyceride/HDL-C)]; AC: atherogenic coefficient [TC-HDL-C/HDL-C]; CRR: cardiac risk ratio (TC/HDL-C). Values are significantly different at P< 0.05. [a]Significantly different from the non-diabetic control [b]and significantly different from diabetic control.

linked to lower HDL-C levels. Diabetes resulted in statistically significant ($P < 0.05$) increased levels of lipid-related atherogenic indicators such as atherogenic index of plasma (AIP), atherogenic coefficient (AC), and cardiac risk ratio (CRR) in diabetic rats (Table 3). Treatment with both PGZ and SY attenuated these lipid alterations and increased atherogenic biomarkers. The effective beast effect was reported by PGZ+ SY in the combination-treated group ($P < 0.05$) for all parameters compared to diabetic untreated rats (Table 3).

Effect on inflammatory and antioxidant statuses

When compared to non-diabetic rats, DM increases ($P < 0.05$) levels of anti-inflammatory markers such as CRP, TNF-α, and IL-6. Furthermore, diabetic rats had higher (P< 0.05) leptin serum levels. DM, on the other hand, induces a substantial ($P < 0.05$) decrease in TAC and PPARɣ expression (Table 4). After treatments with PGZ, SY, and PGZ+ SY, these issues were ameliorated (significant differences varied according to the treatment type; Table 4). As mentioned in previous DM-related

TABLE 4. Anti-inflammatory and antioxidant parameters between untreated and treated rats.

Variables	Non-Diabetic Group	Streptozotocin-induced diabetic groups			
		Control	PGZ	SY	PGZ + SY
	(n = 9)	(n = 9)	(n = 9)	(n = 9)	(n = 9)
CRP (ng/mLL)	2952 ± 856	12188 ± 316[a]	5146.1 ± 316[a,b]	2786 ± 730[b]	4046 ± 515[a,b]
TNFα (pg/mLL)	241.8 ± 1.5	542.1 ± 3.5[a]	402.0 ± 3.3[a]	491.9 ± 89.8[a]	363.3 ± 3.9[b]
IL-6 (pg/mLL)	20.89 ± 0.03	92.71 ± 1.33[a]	53.64 ± 1.17	85.27 ± 2.30[a]	35.36 ± 3.68[b]
TAC (U/mLL)	0.23 ± 0.01	0.15 ± 0.01[a]	0.18 ± 0.01	0.16 ± 0.01[a]	0.20 ± 0.01[b]
PPARɣ (pg/mLL)	305.9 ± 4.6	125.4 ± 1.1[a]	231.8 ± 0.9[b]	170.2 ± 57.3[b]	249.0 ± 54.8[b]
Leptin (ng/mLL)	8.37 ± 0.12	18.04 ± 0.18[a]	9.43 ± 0.02[b]	14.02 ± 0.59[a]	9.28 ± 0.81[b]
Selenium (µmol/mLL)	0.34 ± 0.12	0.31 ± 0.14	0.10 ± 0.06	0.13 ± 0.04	0.23 ± 0.08

Values are the means ± SEM. Abbreviations: PGZ: pioglitazone; SY: selenium-yeast; CRP: C-reactive protein; TNFα: tumor necrosis α; IL-6: interleukin 6; TAC: total antioxidant capacity; PPAR Ɣ: Peroxisome proliferator-activated receptor-gamma. Values are significantly different at P< 0.05. [a]Significantly different from the non-diabetic control and [b] significantly different from diabetic control.

complications, the best effect on anti- inflammatory and antioxidant statuses was reported in the PGZ+ SY combination ($P < 0.05$ for all parameters compared to diabetic untreated rats; Table 4).

DISCUSSION

The intricacy of type 2 diabetes has sparked substantial interest in the development of novel pharmacological therapies to manage the disorder.[20] Owing to its antioxidant and anti-inflammatory features, SY was suggested to possess hypoglycemic properties in DM models.[15] Recently, it has been reported that Se has features that mimic insulin and synergize with other established anti-diabetic drugs on type 2 DM models.[21,22] Furthermore, PGZ is a PPARγ agonist anti-diabetic medicine that was developed for uncoupling undesired hypoglycemia caused by other DM treatments from reducing blood glucose. While α-glucosidase inhibitors efficiently reduced systemic glucose, sulphonylureas, and insulin-regulated communication from the pancreas to peripheral tissues, PGZ opened an alternative road by boosting insulin responsiveness in peripheral tissues.[23] As a result, the present investigation seeks to elucidate the synergistic hypoglycemic effects of SY and/or PGZ as mono- and combination treatment in rats with STZ-induced DM.

In this study, as an accepted diabetic animal model,[21] STZ was used to induce type 2 DM and to explore DM pathophysiology. In experimental animals, STZ causes a β-cell failure, the final event contributing to DM development, so it is used for DM induction.[21] The current study demonstrated that STZ-induced DM and insulin resistance resulted in hyperglycemia, hyperinsulinemia, and elevated HbA1c levels. DM animals treated with PGZ+ SY, on the other hand, had better glycemic control and insulin levels comparable to control rats.

These results were similar to other reported findings.[21,22] This effect might be attributed to Se's' capacity to rejuvenate beta cell function, stimulate insulin secretion, and so reduce blood glucose levels.[21] Se can possess insulin-mimetic effects by activating the insulin signaling cascade Akt and other kinases.[24] Also, other mechanisms may support the Se hypoglycemic effect, including intestinal glucose transport inhibition. Furthermore, in rats, Se has been shown to increase renal glucose excretion.[25] Sodium selenate enhanced glucose uptake in isolated rat adipocytes by activating serine/threonine kinases and translocating glucose transporters

to the plasma membrane, according to an early study.[26,27] Moreover, in STZ-treated rodents, selenate improved glucose homeostasis, and this anti-diabetic effect has been associated with partial reversal of abnormal activity and expression of gluconeogenic and glycolytic liver enzymes.[25]

Similar to previous studies,[21] the existence of insulin resistance (IR) in STZ-induced diabetes was clearly shown by elevated HOMA-IR in this research. The administration of PGZ+ SY together reduced the induced IR in these diabetic animals. These data support SY and PGZ's' synergistic impact on DM-induced hepatic IR and β-cell function augmentation.

In DM, SY was reported to have an essential role in inhibiting lipid dysfunction and its related inhibition of the formation of atherosclerosis.[28] In this study, SY had a synergistic effect when combined with PGZ for effecting beneficial changes in cholesterol, triglycerides, LDL, and HDL levels. It improved related atherogenic biomarkers, including AIP, AC, and CRR. A similar association was reported between adequate Se levels and reduced atherogenic risk.[29]

Regarding DM pathogenesis in human and animal models, many studies elucidate oxidative stress implication as a common factor that causes increasing tissue-specific IR.[21] In addition, hyperglycemia may significantly increase the creation of oxidative stress in tissues, as well as the imbalance between the anti-oxidant protection system and the formation of reactive oxygen species (ROS).[30] Moreover, an association between inflammation and DM is an active research item. Inflammation has previously been linked to the development of diabetes, and hyperglycemia has been linked to an increase in circulating inflammatory markers.[30] Recent animal and human model studies show that inflammation and IR are intimately related throughout the development of diabetes.[21] Thus, it is essential to discover therapies against oxidative and inflammatory stresses as standard treatments for DM.[21]

Experimental studies suggest that Se antioxidant supplements could delay DM development by decreasing oxidative and inflammatory stress.[15] In this study, treatments with PGZ+ SY ameliorated the increase in inflammatory parameters (CRP, TNF-α, and IL-6) and reduced TAC and PPARɣ levels caused by STZ-DM induction. For example, but not limited, Abdulmalek et al. observations demonstrated that Se in nanoparticles form has a synergistic effect with the anti-diabetic drug metformin that resulted in a remarkable protective anti-diabetic effect illustrated by significantly reduced FBG and insulin levels.

At the same time, Se exhibited anti-inflammatory and antioxidant effects by cytokine expression mitigation and increased TAC.[21]

CONCLUSION

Taken together, this study justifies the synergistic effect and anti-diabetic potential of PGZ and SY combined therapy. This medication may postpone the development of STZ- induced diabetes and reduce the risk of complications. This might be accomplished by improving insulin sensitivity and scavenging free radicals. This medication reduced fat buildup induced by high blood glucose levels. Furthermore, it reduced the expression of pro-inflammatory cytokines and restored antioxidant capability.

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This research received no external funding

ETHICAL APPROVAL

All animal experiments were performed as per the guidelines of the National Council for Animal Experimentation Control, and the Ethical Committee approval was obtained from the ethical committee of the University of Jordan, Amman, Jordan.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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