Current Science International
Volume: 10 | Issue: 04| Oct. – Dec.| 2021

EISSN:2706-7920 ISSN: 2077-4435
DOI: 10.36632/csi/2021.10.4.52
Journal homepage: www.curresweb.com
Pages: 623-626

Sitagliptin ameliorates the insulin sensitivity in Skeletal Muscles of Metabolic Syndrome Rat Model

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Received: 10 Oct. 2021 **Accepted:** 15 Nov. 2021 **Published:** 20 Nov. 2021

ABSTRACT

This study aims to test the hypothesis that sitagliptin can effectively ameliorate the insulin sensitivity in the skeletal muscles of metabolic syndrome rat model. Rats were fed either standard diet (Control group) or high fat diet (HFD) and 20% fructose (w/v) in the drinking water (HFFD). After 12 weeks, a group of HFFD animals received a daily oral dose of 10 mg/kg b.w. of sitagliptin for another 4 weeks. Sitagliptin improved the hyperglycemia, hyperinsulinemia and insulin sensitivity of the skeletal muscle. Also improved the protein levels of insulin receptor (IR) and glucose transporter 4 (GLUT4).

Keywords: Metabolic syndrome, insulin, sitagliptin

1. Introduction

As a result of the increased consumption of sugar-rich and fatty-products, and the increase in preference for such products, metabolic disorders are becoming more common at a younger age. Metabolic syndrome is a multifaceted metabolic disorder. It includes insulin resistance, weight gain, hypertriglyceridemia and high blood pressure. According to WHO, the prevalence of metabolic syndrome was 17.1% all over the world (Bocarsly *et al.,* 2010; Heyn *et al.,* 2019). It also affects the peripheral tissues to respond to insulin. One of these tissues is the skeletal muscle (SM) which use glucose under insulin-stimulated conditions (DeFronzo and Tripathy, 2009).

Recent epidemiological studies of sugar consumption and diabetes prevalence (Basu *et al.,* 2013) suggest that a diet rich in fat as well as sugar is a greater risk factor for the metabolic disorders than a diet that is rich in either fats or sugars (Lozano *et al.,* 2016).

The therapeutic options of metabolic syndrome are limited to treat each of its components separately and no single therapy approved to manage it (McCracken *et al.,* 2018). Dipeptidyl peptidase-4 inhibitors (DPP-4i) or gliptins are double-acting enhancers that both stimulate insulin secretion and reduce glucagon secretion in a glucose-dependent manner. So, the present study was designed to investigate the role of sitagliptin on the insulin action in the SM using insulin-resistant rat model induced by high fat and high fructose.

2. Materials and methods

Thirty adult male rats were obtained from the Egyptian Organization for Biological Products and Vaccines, Egypt. Rats were harbored in stainless steel cages (5/cage) and were acclimatized for a week with standard conditions of humidity, temperature and 12h light and dark cycles with food and water ad libitum.

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Rats were divided into 3 groups (10 rats each): rats fed on standard diet for 4 months as a control group (NC). High fat and high fructose diet group (HFFD): rats fed on a high fat diet and 20% fructose drinking water for 4 months (Gancheva *et al.,* 2015; Lozano *et al.,* 2016). Sitagliptin treated group: rats fed High fat and high fructose, and at the thirteenth week they received a daily oral dose of 10mg/kg body weight sitagliptin (Dennison *et al.,* 2017).

Blood samples after overnight fasting were centrifuged at 4000 rpm for 5min and serum was separated. Femoral muscle was excised immediately, washed with cold PBS (pH 7.4) and dried by filter paper.

Serum glucose was assayed by colorimetric method with commercially kit (SPINREACT, Spain), while serum insulin was assayed by enzyme-linked immunosorbent assay kit (DRG, USA). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated (Antunes et al. 2016). The protein level of muscular insulin receptor (IR), and glucose transporter-4 (GLUT-4) were detected by western blot assay according to the manufacturer's instruction using β-actin as a control.

2.1. Statistical analysis

Data are expressed as mean ± standard error of mean (SE). Differences between the mean values were assessed by one-way analysis of variance (ANOVA) and followed by Tukey's Kramer multiple comparison test and GraphPad Prism 5 software. The p-value <0.05 was considered significant. The statistical analyses were applied using the statistical package for social sciences software (SPSS, Chicago, IL, USA) version 16.

3. Results

Significant elevations ($p<0.0001$) in fasting serum glucose and insulin levels in rats fed HFFD were observed as compared to control rats (Table 1). Administration of sitagliptin significantly reduced these tested parameters, compared to the HFFD group. Data in Table 1 illustrate a significant elevation in HOMA-IR value ($p<0.0001$) in the HFFD group, compared to control. While, these levels were reduced significantly by sitagliptin, compared to NC group.

Muscular IR and GLUT-4 proteins were significantly reduced in the HFFD group, compared to control (Table 1). Surprisingly, sitagliptin treated group showed non-significant elevation in IR and GLUT-4 protein levels, compared to HFHFD group.

Table 1: Serum levels of glucose and insulin and HOMA-IR (mean ± SE) in the different experimental groups

Variables \ Groups	Control	HFFD	Sitagliptin
Glucose (mg/dL)	113.30 ± 15.50	260.30 ± 42.40[a]	154.80 ± 20.10[b]
Insulin (µIU/L)	8.43 ± 0.45	18.00 ±1.19[a]	13.40 ± 0.81[b]
HOMA-IR	2.33 ± 0.08	11.34 ± 0.46[a]	5.04 ± 0.18[b]
IR	1.00 ± 0.00	0.59 ± 0.07[a]	0.65 ± 0.04
GLUT-4	1.00 ± 0.00	0.35 ± 0.04[a]	0.50 ± 0.04

a: Significance versus control, b: Significance versus HFFD.

4. Discussion

The present model of high fat/fructose consumption for 16 weeks successfully induced metabolic syndrome as proved by the elevated level of serum glucose and insulin resistance index. The insulin resistance was higher in HFFD group as illustrated by the higher value of HOMA-IR (11.43), which was greater than the cut-off point (2.29) (Radikova *et al.,* 2006), indicating severe insulin resistance. These results are in line with previous studies (Ahmed *et al.,* 2018; Mohamed *et al.,* 2019).

The ameliorative effect of sitagliptin on the state of insulin resistance was also proved by improving the insulin sensitivity. These results agree with previous studies (Ramírez *et al.,* 2018; Prakash *et al.,* 2020) that reported that sitagliptin restores the insulin sensitivity.

High dietary fat/fructose intake represents one of the earliest causes associated with the reduction of skeletal muscles' sensitivity to insulin (Lark *et al.,* 2012). In the current study, insulin action was substantially impaired in skeletal muscles of HFFD fed rats as illustrated by the reduction

of IR and GLUT4 protein levels in, consequently reduced the membrane translocation of GLUT4 and cellular glucose uptake. These results are in line with previous studies (Liu *et al.,* 2018; Li *et al.,* 2020). The chronic exposure to fructose can indirectly create compensatory hyperinsulinemia with insulin resistance due to a down regulation of insulin receptors with lower expression of insulin receptor mRNA in the liver, adipose tissue, and skeletal muscles (De Castro *et al.,* 2015)

Although non-significant elevations were observed in GLUT4 and IR levels in skeletal muscle of treated rats with sitagliptin, but it also showed non-significant change as compared to control rats, which is confirmed by the improvement of insulin sensitivity as indicated by the reduction of HOMA-IR and glucose. The elevation of GLUT4 protein content and its translocation to the cell membrane of peripheral insulin target tissues are responsible for improvement in sensitivity to insulin action (Si *et al.,* 2012).

5. Conclusion

The findings of the present study indicate the efficacy of sitagliptin in improving insulin sensitivity in skeletal muscles of rats feeding high-fat and fructose as a model of metabolic syndrome.

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