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Beneficial effect of sitagliptin on high fat diet induced obesity in wistar rats

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ABSTRACT

Purpose: Obesity is one of the rising health problems and has become a major concern with highest prevalent global epidemiology. Various evidences suggest that the action or effect of glucagon-like-peptide-1 (GLP-1), which acts as a satiety signal may be impaired in obese subjects. Dipeptidyl peptidase-4 (DPP-4) is the principal enzyme that metabolizes GLP-1 and sitagliptin, a DPP-4 inhibitor which prevents the breakdown of GLP-1. Thus the purpose of the present study was to investigate the beneficial effect of sitagliptin, a DPP-4 inhibitor on body weight gain, adiposity and biochemical anomalies in rats.

Materials and methods: In the present study chronic administration of sitagliptin (10, 20 and 40 mcg/kg/day p.o) for 6 weeks along with high fat diet to the obese rats which were pretreated with high fat diet feeding for 4 weeks on the various parameters of obesity were analyzed. Their effects on body weight, feed intake (kcal), weight and size of fat pads, levels of serum glucose, triglycerides, total cholesterol, high density lipoproteins (HDL) and low density lipoprotein were analyzed.

Results: Treatment with sitagliptin (10, 20 and 40 mcg/kg/day p.o) produced significant dose dependent decrease ($p < 0.05$) in body weight gain, feed intake (kcal), weight and size of fat pads, levels of serum glucose, triglycerides, total cholesterol and low density lipoproteins as compared to high fat diet group. Moreover level of serum high density lipoproteins were increased as compared to high fat diet group. Sitagliptin, a DPP-4 inhibitor positively modulates the parameters of obesity and the effect was comparable to orlistat, a well reported drug for obesity.

1. Introduction

Obesity is a chronic medical condition that affects all organ systems due to accumulation of body fat in the body to such an extent that it increases the risk of a variety of comorbid conditions, including type-2 diabetes, hypertension, dyslipidaemia, cardiovascular disease, obstructive sleep apnea, nonalcoholic fatty liver disease, osteoarthritis, and some types of cancer. Fortunately, even modest weight loss (e.g., 5–10% of initial body weight) can reduce the severity of existing complications and prevent the development of new ones. Overweight and obesity are independent risk factors for increased morbidity and mortality throughout the lifecycle. It is estimated that upto 90% of individuals with type 2 diabetes are obese or at the verge of getting obese (Allison and Saunders, 2000). Obesity is widespread not only in developing countries but also in the developing world with over 115 million people suffering from obesity related problems. In recent years, there has been an increased understanding and appreciation of the role of gastrointestinal hormones in the control of glucose metabolism and regulation of body weight. One such hormone, GLP-1, is produced primarily by enteroendocrine L-cells located in the ileum, although these cells are also present throughout the small intestine and colon. GLP-1 is secreted in response to food intake and the presence of nutrients in the intestinal lumen (Drewnowski, 2007). GLP-1, along with other gut peptides, is responsible for the phenomenon known as the incretin effect, in which the response of insulin to an oral glucose load exceeds that elicited by an equivalent amount of glucose delivered intravenously. GLP-1 also plays a role in the ileal brake mechanism, in which the presence of nutrients in the ileal lumen leads to a decrease in gastric motility. The GLP-1 receptor belongs to the G-protein coupled family of receptors, and it is known to be present in the pancreas, gastrointestinal tract, brain, and other tissues, including the heart (Gallwitz, 2007). GLP-1 receptors have also been identified in vagal

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afferent neurons in the rat nodose ganglion, and studies suggest that GLP-1 may act on target organs not only through classic hormonal mechanisms but also through neural pathways (James et al., 2001). In the pancreas, important actions of GLP-1 include the enhancement of glucose-dependent insulin synthesis and secretion, and stimulation of beta-cell proliferation (James et al., 2000). GLP-1 also inhibits inappropriate alpha-cell glucagon secretion, which occurs despite hyperglycemia in patients with type 2 diabetes (Levin and Triscari, 1983a). This reduction of glucagon secretion reduces hepatic glucose output and contributes to the antidiabetic effects of GLP-1. Important gastrointestinal effects of GLP-1 include reductions in gastric acid secretion and gastrointestinal motility, both of which are mediated primarily through the vagus nerve (Mentlein, 1999a, 1999b). In the brain, GLP-1 receptors are found in the paraventricular nucleus and other hypothalamic regions involved in the regulation of appetite.

Various central and peripheral mediators are involved in pathogenesis of obesity i.e. GLP-1, Oxyntomodulin, CCK. Alteration in the concentrations of these mediators can be the target for obesity treatment. Sitagliptin, a dipeptidyl peptidase inhibitor (DPP-4 inhibitor) that has recently been approved for the therapy of type 2 diabetes, binds to DPP-4 and prevents the breakdown of glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) (Must et al., 1999). Both GLP-1 and GIP are types of incretin hormones released by the intestines that stimulate insulin secretion from β cells (Schmidt et al., 1985) and suppress glucagon secretion. GLP-1 and GIP are rapidly broken down by DPP-4 (Surya et al., 2009). GLP increases the satiety not only n rodents but also in humans by increasing the gastric emptying time & by other central mechanisms (Gül et al., 2011). DPP-4 enzyme metabolizes GLP-1 and improves its concentration on inhibition (Dansinger et al., 2005). This enables a two-to three-fold increase in endogenous GLP-1 thus augmenting its insulinotropic and glucagon inhibiting effects. Sitagliptin, a DPP-4 inhibitor may be a good anti obesity drug (Brinkworth et al., 2008). Sitagliptin has also shown to possess anti-obesity effect in humans in various studies indicating its use in weight loss (Soliman et al., 2013). Thus the purpose of present study was to explore the effect of Sitagliptin on high fat diet induced obesity in wistar rat.

2. Material and method

CHEMICALS: Casein (Modern Dairy, New Karnal, India) and cholesterol (Thomas Baker, Mumbai, India) was used to prepare high fat diet. Orlistat (Macleod's Pharmaceuticals Ltd Mumbai 400059, Batch no. TT901) was dissolved in distilled water. Sitagliptin (MSD pharmaceuticals Pvt Ltd Puducherry Batch no.GN901) was dissolved in water. All drug solutions were freshly prepared before use.

Animals and experimental design: Male Wistar rats, weighing 150-200 gm were employed in the present study and were fed on standard chow diet or high fat diet. Food and water were provided *ad libitum* throughout experimental period. They were housed in departmental animal house and were exposed to 12 h light and 12 h dark cycles. The experimental protocol used in the present study was approved by Institutional Animal Ethics committee. About 48 rats were divided into eight groups.

- Group 1: Normal Control
- Group 2: Orlistat 30 mg/kg/day (Standard chow)*
- Group 3: Sitagliptin 20 mcg/kg/day (Standard chow)*
- Group 4: High Fat Diet*
- Group 5: Orlistat 30 mg/kg + High Fat Diet*
- Group 6: Sitagliptin 10 mcg/kg/day + High Fat Diet*
- Group 7: Sitagliptin 20 mcg/kg/day + High Fat Diet*
- Group 8: Sitagliptin 40 mcg/kg/day + High Fat Diet*

(* = Fourth week and continued up to the end of the tenth week)

Orlistat and sitagliptin were administered by oral route. Obesity was produced by feeding high fat diet and mineral mix to rats for a period of 10 weeks. The high fat diet contained 5.33 Kcal/gm while the normal chow contains 3.80 Kcal/gm.

2.1. Assessment of anthropometric parameter

The increase in the body weight, as compared to age matched control group, was regarded as obesity. Body mass index (BMI) i.e. weight (g)/height (cm)^2, Lee index i.e. (Body Wt)$^{1/3}$/ano-nasal length (cm) x 1000 were calculated before and after the treatment as an index of obesity (Novelli et al., 2007). Body weight was assessed twice in a week. The intake of food by individual rats was also recorded twice a week. To evaluate the effect of high fat diet and drug treatment, adipose tissue were isolated, freed from surrounding tissue, weight individually and after that total weight was calculated. In addition to this, the liver was also isolated, freed from surrounding tissues and was weighed.

2.2. Assessment of biochemical parameter

The hyperlipidemia was assessed by estimating the levels of total cholesterol, HDL, LDL, VLDL and triglycerides in blood serum using commercial available kits. Values were expressed in mg/dl.

Statistical Analysis: Results were expressed as mean ± S.D. The data obtained from various groups were statistically analyzed using one-way ANOVA followed by Tukey's multiple comparison tests. The p-value that came out was (< 0.05) is considered to be statistically significant.

3. Results

Obesity was produced by high fat diet (58% calories as fat, 25% protein and 17% carbohydrate, as percentage of total Kcal) and various parameters of obesity were assessed by comparing results obtained from different groups.

3.1. Effect of various pharmacological interventions on anthropometric parameters

In high fat diet model, a significant increase ($p < 0.05$) in body weight, body mass index, Lee index, feed consumption (Kcal); and decrease in feed consumption (in gram) were observed in rats fed over high fat diet, as compared to age matched normal rats fed on standard diet and Orlistat which was positive control in present study decreases all the anthropometric parameters of obesity (Table no1). Treatment with Sitagliptin administrations in high, medium and low doses produced significant decrease ($p < 0.05$) in body weight, body mass index (BMI) and Lee index as compared to HFD control group and the result was very near to the positive control group i.e. HFD + Orlistat. There was no significant *perse* effect of Sitagliptin and Orlistat.

Table 1
Effect of normal diet and HFD on the body weight, body mass index, lee index, feed intake in gram and feed intake in Kcal.

Parameter	Normal control	High fat diet	HFD + Orlistat
Initial Body weight (gm)	205.83 ± 13.93	201.66 ± 8.16	209.16 ± 14.28
Final Body weight (gm)	253.33 ± 14.7	353.33 ± 8.25[a]	240 ± 15.16[b]
Body mass index (g/cm^2)	0.83 ± 0.05	1.17 ± 0.05[a]	0.79 ± 0.04[b]
Lee index (gm/cm)	362.85 ± 11.31	407.80 ± 9.91[a]	359.7 ± 8.27[b]
Feed intake (gm)	18.47 ± 1.78	17.91 ± 1.86[a]	12.7 ± 1.34[b]
Feed intake (Kcal)	70.57 ± 6.79	95.49 ± 9.95[a]	68.10 ± 7.19[b]

The body mass index symbol is the mentioned one. And super script denotes the level of significance between groups.

Table 2
Effect of normal diet and HFD on the various fat deposits.

Parameter	Normal diet control	High fat diet	HFD + Orlistat
MES (gm)	1.66 ± 0.85	7.67 ± 1.12[a]	2.37 ± 0.47[b]
RET (gm)	1.25 ± 0.54	7.51 ± 0.87[a]	2.50 ± 0.40[b]
EPI (gm)	2.27 ± 0.31	7.08 ± 0.59[a]	2.42 ± 0.39[b]
TF (gm)	5.20 ± 1.21	22.26 ± 1.73[a]	7.30 ± 1.26[b]

The body mass index symbol is the mentioned one. And super script denotes the level of significance between groups.

3.2. Effect of various pharmacological interventions on different fat deposits

Administration of high fat diet (HFD) for 10 weeks caused a significant ($p < 0.05$) increase in body fat depots: epididymal, retroperitoneal, mesenteric fat depots and total fat depot (Table no 3). Treatment with Sitagliptin administration produced significant decrease ($p < 0.05$) in body fat depots: epididymal, retroperitoneal, mesenteric fat depots and total fat in comparison to HFD control (Table no 4). There was no significant *perse* effect of Sitagliptin and Orlistat on this parameter.

3.3. Effect of various pharmacological interventions on serum biochemical parameters

There was a significant ($p < 0.05$) increase in serum concentration of cholesterol, triglycerides, LDL, VLDL and decrease in HDL in HFD control group as compared to normal animals on standard diet. Orlistat which was positive control in present study decreases all the biochemical parameter of obesity (Table no-2). Treatment of HFD rats with Sitagliptin administration in low, medium and high doses produced a significant decrease ($p < 0.05$) in serum level of glucose, total cholesterol, triglyceride, VLDL, LDL and significant increase in the level of HDL as compared to HFD control group and the result was very near to the positive control group i.e. HFD + Orlistat. (Table no-3). There was no significant *per se* effect of Sitagliptin and Orlistat on this parameter.

4. Discussion

The present study was undertaken to determine the effect of Sitagliptin on high fat diet treated rats and effect was compared with the standard drug used in obesity called Orlistat. It was observed that Sitagliptin affects the alteration of various parameters of obesity positively.

Obesity is a medical condition in which excess body fat accumulates and poses numerous adverse effects in our body. The global epidemiology of overweight and obesity is one of the most important public health problems due to its common associations with many chronic diseases like type 2 diabetes, cardiovascular disease, hypertension, dyslipidemia, gallbladder disease, certain cancers, and respiratory problem (James et al., 2001). Body mass index (BMI) is considered as a convenient, accurate and low cost measurement for estimating the prevalence of obesity while waist circumference (WC) is recommended for measuring abdominal adiposity. Therefore, BMI in combination with WC may allow more precise epidemiological monitoring of overweight and obesity (Booth et al., 2000). Obesity is caused by a chronic energy imbalance involving both dietary intake and physical activity patterns. These behavioral patterns and their environmental determinants are identified as complex, important factors for obesity (Swinburn et al., 2011). HFD fed rats exhibited significant increase in body weight, plasma glucose, insulin, triglycerides and total cholesterol level as compared to normal diet fed control rats (Novelli et al., 2007). The extent of metabolic disorder induced by the respective diet depends more on the specific rodent strains and the dietary regimen employed on the species itself. For e.g. C57BL/6J mice develop obesity (Levin and Triscari, 1983b). The lipogenesis was upregulated by HFD in rats lead to elevation of plasma lipids (Storlien et al., 1986) which is characterized by elevated TG levels, LDL-C levels and decreased serum HDL-C (Kutoh and Yamashita, 2012) in obese rats. Further, feeding with high fat diet caused hyperglycemia in rats (Ikemoto et al., 1995). Therefore the serum lipid levels (total cholesterol, LDL, VLDL, HDL, and triglycerides) and glucose levels were estimated in present study as the marker of hyperlipidemia and hyperglycemia (Monami et al., 2012). In present study high fat diet (HFD) induction for 10 weeks leads to obesity and dyslipidemia as evident by gain in body weight, increased feed intake (Kcal), body mass index, lee index and decreased feed intake (in grams) increase in triglyceride levels. This effect may due to increased fat accumulation and impaired glucose metabolism. In the present study, treatment with Sitagliptin attenuates the effect of HFD treatment.

Sitagliptin is a dipeptidyl-peptidase inhibitor (DPP-4 inhibitor). Its action is mediated by increasing levels of the incretin hormones like glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP).Sitagliptin was given at the dose of 10 mcg/kg, 20 mcg/kg and 40 mcg/kg oral to HFD treated rats at the end of fourth week and continued up to the end of tenth week. Various physical parameters such as body weight, Body mass index, Lee Index, were assessed. Several biochemical parameters such as cholesterol, very low density lipoproteins, low density lipoproteins, triglycerides and glucose levels were also determined. In present investigation it has been observed that administration of Sitagliptin in low, medium and high dose for 6 weeks to the high fat diet fed animals significantly decreased the markers of obesity as compared to HFD control group and the effect was found to be increased in dose dependent manner. We examined that sitagliptin reduced body adiposity with diet induced obesity. Sitagliptin decreased body weight dose dependently. The high dose of Sitagliptin was found to be more effective as compared to its medium and low dose indicating that sitagliptin prevents the progression of obesity from predisposed factors. Sitagliptin mainly decreases the feed intake which proves that it may act through peripheral mechanism. Sitagliptin decrease the body weight, BMI, Lee index, Feed intake (in kcal), as compared to HFD treated rats. In the present study due to the administration of Sitagliptin

Table 3
Effect of various pharmacological interventions on the body weight, body mass index, lee index, feed intake in gram and feed intake in Kcal.

Parameters	Initial Body weight (gm)	Final Body Weight (gm)	Body mass Index (gm/cm^2)	Lee index (gm/cm)	Feed intake (gm)	Feed Intake (Kcal)
Normal diet treatment						
Normal diet control	205.83 ± 13.93	253.33 ± 14.7	0.83 ± 0.05	362.85 ± 11.31	18.47 ± 1.78	70.57 ± 6.79
Orlistat-*per se*	200.83 ± 10.20	209.16 ± 12.41	0.70 ± 0.03	343.49 ± 6.94	19.27 ± 1.65	68.75 ± 8.81
Sitagliptin –*per se* (high)	200 ± 14.14	206.66 ± 12.9	0.69 ± 0.02	342.19 ± 7.65	17.18 ± 1.15	65.29 ± 4.40
High fat diet treatment						
High fat diet	201.6 ± 8.16	353.33 ± 8.25[a]	1.17 ± 0.05[a]	407.8 ± 9.91[a]	17.91 ± 1.86[a]	95.49 ± 9.95[a]
HFD + Orlistat	209.16 ± 14.28	240 ± 15.16[b]	0.79 ± 0.04[b]	359.7 ± 8.27[b]	12.7 ± 1.34[b]	68.10 ± 7.19[b]
HFD + Sitagliptin (low)	204.16 ± 12.81	246.66 ± 16.02[b]	0.82 ± 0.05[b]	363.24 ± 11.36[b]	16.08 ± 2.10[b]	85.72 ± 10.71[b]
HFD + Sitagliptin (medium)	200 ± 12.64	244.16 ± 12.11[b]	0.79 ± 0.04[b]	359.29 ± 12.39[b]	13.73 ± 1.55[b]	73.19 ± 8.26[b]
HFD + Sitagliptin (High)	204.16 ± 12.00	228.33 ± 5.16[b]	0.73 ± 0.04[b]	347.24 ± 11.03[b]	12.2 ± 0.79[b]	65.02 ± 4.23[b]

The body mass index symbol is the mentioned one. And super script denotes the level of significance between groups.

Table 4
Effect of various pharmacological interventions on the various fat deposits.

Parameters	MES	RET	EPI	TF
Normal diet treatment				
Normal diet control	1.66 ± 0.85	1.25 ± 0.54	2.27 ± 0.31	5.20 ± 1.21
Orlistat – *per se*	1.86 ± 0.94	1.80 ± 0.85	2.04 ± 0.73	5.71 ± 2.38
Sitagliptin – *per se*	2.38 ± 0.24	2.41 ± 0.30	2.28 ± 0.21	7.07 ± 0.43
High fat diet treatment				
High fat diet	7.67 ± 1.12[a]	7.51 ± 0.87[a]	7.08 ± 0.59[a]	22.26 ± 1.73[a]
HFD + Orlistat	2.37 ± 0.47[b]	2.50 ± 0.40[b]	2.42 ± 0.39[b]	7.30 ± 1.26[b]
HFD + Sitagliptin (low)	3.14 ± 1.35[b]	4.09 ± 0.59[b]	4.01 ± 0.67[b]	11.20 ± 1.73[b]
HFD + Sitagliptin (medium)	3.15 ± 0.65[b]	3.07 ± 0.67[b]	3.00 ± 0.76[b]	9.22 ± 2.03[b]
HFD + Sitagliptin (high)	2.67 ± 0.87[b]	2.86 ± 1.04[b]	2.69 ± 0.85[b]	8.23 ± 2.49[b]

The body mass index symbol is the mentioned one. And super script denotes the level of significance between groups.

level of serum LDL, TG, TC were reduced with enhanced levels of HDL. Sitagliptin decreases weight of epididymal, mesenteric, retroperitoneal fat in adipose tissues.

Hence, it was observed that Sitagliptin plays beneficial role in obesity; providing a rational pharmacological basis for its use in obesity in man.

5. Conclusion

In conclusion, it has been observed that Sitagliptin plays major beneficial role in reducing obesity; and the study served as a rational pharmacological basis for the use of Sitagliptin in obese patients with type 2 diabetes.

Conflicts of interest

The author declares no conflict of interest in preparing the present review.

Contribution of authors

The role of all the authors in the studies is as follows:

AG: Observations were recorded by the author.

TB: The author read and approved the final manuscript.

RM, SM: Both the authors organized the data and made appropriate amendments and citations in the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.obmed.2019.100084.

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