The Effect of High Fat Diet and High Fructose Intake on Insulin Resistance and GLP-1 in Experimental Animals

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Abstract

Glucagon like peptide-1 (GLP-1) is an incretin hormone which is responsible for insulin secretion in response to hyperglycemia. GLP-1 secreted from intestinal cells, inhibits glucagon secretion and suppresses food intake in both diabetic and nondiabetic humans. Both high fat diet, high fructose intake contribute to development of insulin resistance. Also the effect of insulin resistance on plasma lipid profile, plasma GLP1 levels and systolic blood pressure.

Aim of Work: To investigate the effect of high fat diet & high fructose intake on inducing insulin resistance, plasma lipid profile, systolic blood pressure and the potential effect of insulin resistance on GLP-1 level.

To achieve this: Thirty male adult white albino rats (weight ranged from 150-250 gm) were randomly divided into 3 groups of 10 animals each:
Group 1: Control normal group.
Group 2: Animals received high fat diet (HFD) 42% providing 70% of calories as fat for four weeks.
Group 3: Animals received normal diet and high fructose concentration of 60% fructose for five weeks.

At the end of the experimental period, these rats were taken for measurement of blood pressure, fasting blood samples were collected for the study of different parameters in plasma, including insulin, glucose, lipid profiles [total cholesterol (TC), triglycerides (TGs), HDL, LDL], also post-prandial plasma for the study of GLP-1 level and measurement of HOMA test was taken as an indicator of insulin resistance.

Results of the present study showed the development of insulin resistance with high fat diet and high fructose intake. In both insulin resistant groups, there was significant elevation of fasting plasma glucose, fasting plasma insulin, fasting plasma (cholesterol, triglycerides and LDL levels). On the contrary, there was highly significant reduction of post-prandial plasma GLP-1 and fasting plasma HDL levels in comparison with control group. There was also rise of systolic blood pressure in insulin resistant rats.

Conclusion: That consumption of excess fat, high fructose intake in diet, play a role in increasing incidence of insulin resistance and the reduction of post-prandial plasma GLP-1 level in insulin resistant rats.

Key Words: GLP-1 – High fat & fructose intake – Insulin resistance.

Introduction

INCRETINS are hormones released from the gastrointestinal tract in response to nutrient ingestion that potentiate glucose-stimulated insulin secretion from islet beta cells [1]. The 2 predominant incretins are glucagon-like peptide (GLP)-1 and glucose-dependent insulinoimotropic peptide (GIP). These 2 peptides stimulate insulin secretion and unlike other insulinoimotropic agents, they do so in a glucose-dependent manner. In light of these beneficial actions, GLP-1 and GIP represent potential therapeutic agents for the treatment of type 2 diabetes. However, exogenous GIP is comparatively less effective than GLP-1 in stimulating insulin secretion in type 2 diabetes (T2DM), whereas the insulinoimotropic action of GLP-1 is well preserved [2]. So much of the current research has focused on enhancing GLP-1 action for the treatment of type 2 diabetes.

GLP-1 also exerts a number of other biological actions that contribute to its ability to lower glucose, including inhibition of gastric emptying, which reduces meal-associated increase in glycemic excursion. Furthermore, GLP-1 has the potential to preserve or enhance beta-cell function in human subjects with type 2 diabetes due to its ability to stimulate beta-cell proliferation and neogenesis and inhibit apoptosis [3].

The major therapeutic drawback in using native GLP-1 is its very short half-life of less than 2 minutes following exogenous administration, due in part to the protease dipeptidyl peptidase (DPP)-IV [4]. As a result of preventing the degradation
of native GLP-1 through inhibiting the activity of the DPP-IV enzyme, this offers a therapeutic strategy for enhancing endogenous GLP-1 action in vivo.

DPP-IV is a ubiquitously expressed serine protease that exhibits postproline or alanine peptidase activity, thereby generating biologically inactive peptides via cleavage at the N-terminal region after X-proline or X-alanine [5]. Because both GLP-1 and GIP have an alanine residue at position 2, they are substrates for DPP-IV. DPP-IV inhibitors are orally administered drugs that improve glycemic control by preventing the rapid degradation of incretin hormones, thereby resulting in postprandial increase in levels of biologically active intact GLP-1 and GIP.

Type 2 diabetes (T2DM) is characterized by a gradual progressive decline from near absent first-phase glucose-induced insulin secretion to impaired second-phase insulin secretion, glucose potentiation, and disproportionate hyperproinsulinemia, with impaired basal or steady state insulin secretion [6]. Patients with clinical disease and fasting hyperglycemia are at the end stage of this process and demonstrate all of these features.

Impairment in the incretin response may contribute to dysregulation of insulin and glucagon secretion, particularly during the postprandial period, leading to hyperglycemia. Evidence suggests that the impaired incretin response in patients with T2DM may be due to decreased GLP-1 levels following food ingestion, which cannot be attributed to enhanced clearance [7].

Material and Methods

Thirty male adult white albino rats (weight ranged from 150-250 gm) were used in the present study. These rats received veterinary care in the animal house of Kaser El-Aini Faculty of Medicine Cairo University.

Animals were allowed to acclimatize to their environment for five days before start of the experiments. All animals were kept under the same environmental conditions and had free access to water and food all through the day time. Rats were randomly divided into 3 groups. Each group comprised 10 rats live in a separate cage in room temperature (24ºc) with day and night cycle.

Group 1:

Control group receiving normal rodent chew and drinking normal water without any additives. The rodent chow was a low fat diet (Providing 10% of calories as fat).

Group 2:

Each animal received high fat diet 42% and drinking normal water. High fat diet (HFD) providing 70% of calories as fat, which was obtained by mixing 42% of fat per 100g of rat chow (28gm of lard and 14gm of corn oil). This group received HFD for five weeks (Research Diet. Lane New Brunswick).

Group 3:

Each animal received normal diet and drinking water with high fructose concentration of 60% (which means that for each 100ml water, 60 gram of fructose was added). Fructose was manufactured by (Panreac Quimica SA). This group received water with high fructose concentration for four weeks. Systolic blood pressure was measured in all rats using the tail-cuff method at the beginning and at the end of experimental period. Blood samples were then collected.

Blood sample collection: By retro-orbital technique using heparinized capillary tubes after an over-night fast, fasting blood samples for measurement of all parameters (except GLP1). The blood samples were delivered into centrifuge tubes to which anticoagulant was added then centrifuged at 10,000 rpm for 20 minutes and plasma was separated and stored at −70ºc. The plasma in fasting state was then used for further determination of plasma level of glucose, insulin, cholesterol, TG, HDL, LDL and post-prandial plasma was used for determination of GLP1, since level of GLP1 in fasting state is undetectable [4]. Measurement of HOMA test was taken as an indicator of insulin resistance.

- Measurement of fasting plasma insulin:

Insulin concentrations were measured in previously frozen plasma samples by enzyme immunoassay using the rat insulin (Enzyme linked immuno sorbant assay) ELISA kit (Linco research).

- Measurement of fasting plasma glucose:

The plasma glucose was assayed by the method adopted by [8]. The test materials for this method were supplied as kits by "Diamond Diagnostics".

- Homeostasis model assessment of insulin resistance (HOMA):

HOMA is an indirect method for the assessment of insulin resistance devised by Matthews et al.,
[9]. It depends on relationship between fasting plasma glucose and insulin based on a mathematical model:

\[
\text{HOMA-IR} = \frac{\text{Fasting glucose (mmol/L) X Fasting insulin (uIU/ml)}}{22.5}
\]

In cases when HOMA is more than 4.0 this diagnosis of insulin resistance [10].

- Measurement of fasting plasma total cholesterol, high density lipoprotein cholesterol (HDL-C), low lipoprotein cholesterol:


- Measurement of fasting plasma triglyceride:

Fasting plasma TG was assayed by the method adopted by Wahlefeld 1974 [12]. Triglyceride quantification kit was used to supply the test materials for this method (BioVision Research).

- Measurement of plasma glucagon like peptides (GLP1):

The GLP-1 ELISA was developed as a quantitative ELISA kit with high specificity and sensitivity (detection limit 0.206ng/mL) for rat/mouse/human GLP-1 in order to be a useful tool for this research.

This EIA kit is used for quantitative determination of rat/mouse/human GLP-1 in plasma samples. The kit is characterized by sensitive quantification, high specificity, and no influence from other components in plasma samples.

The GLP-1 standard is a highly purified synthetic product.

The EIA kit has high specificity to rat/mouse/human GLP-1 and shows no cross-reactivity with rat/human/mouse glucagon, human glicentin, or rat/mouse/human GLP.

Systolic blood pressure measurement:

Systolic blood pressure in rats was measured by Harvard rat tail blood pressure monitor system. This system is an electronic version of the traditional sphygmomanometer cuff method, used to determine human blood pressure indirectly.

Statistical analysis:

Data were statistically described in terms of range, mean and standard deviation (± SD). Comparison of quantitative variables between the study groups was done using ANOVA test (analysis of variance). A probability value (p-value) less than 0.05 was considered statistically significant [13].

Results

Glucose, insulin levels an homeostasis model assessment (HOMA) values in different experimental groups studied were shown in Table (1) and Figs. (1-3). It can be seen that there was highly significant increase in plasma glucose, insulin levels and in homeostasis model assessment (HOMA) values in high fat diet group and in high fructose concentration if compared with their control animals.

| Table (1): Levels of glucose, insulin, HOMA in studied groups. |
|-----------------|---------------------|---------------------|---------------------|
| Item            | Control group (Group 1) | High fat diet group (Group 2) | High fructose concentration group (Group 3) |
| GLUCOSE (mmol/L)| Mean±SD              | Mean±SD              | Mean±SD              |
| 8.19±1.29*     | 10.75±1.61*          |                     |
| INSULIN (µIU/ml)| 16.91±3.64*         | 19.30±3.80$          |
| HOMA            | 2.04±0.21            | 6.26±2.18*           | 9.21±2.43*          |

* Significant p as compared to control group (Group 1) (p<0.001).
$ Non Significant p as compared to high fructose concentration (Group 3) (p>0.05).

Table (2): Comparison of plasma glucose, plasma insulin and HOMA levels between high fat diet group (Group 2) and high fructose concentration (Group 3).

<table>
<thead>
<tr>
<th>Item</th>
<th>High fat diet group (Group 2)</th>
<th>High fructose concentration group (Group 3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUCOSE (mmol/L)</td>
<td>10.75±1.61*</td>
<td>8.19±1.29*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INSULIN (µIU/ml)</td>
<td>19.30±3.80$</td>
<td>16.91±3.64*</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HOMA</td>
<td>9.21±2.43*</td>
<td>6.26±2.18*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Significant p as compared to high fructose group (Group 2) (p<0.001).
$ Non Significant p as compared to high fructose group (Group 2) (p>0.05).

Fig. (1): Comparison of plasma glucose in studied groups.

* Significant p as compared to control group (Group 1) (p<0.001).
+ Significant p as compared to high fat diet group (Group 2) (p<0.001).
Table (2) revealed that the mean values of glucose and glucose HOMA test, are significantly increase in the high fat diet group than the high fructose intake group. But not significant with insulin.

There is positive correlation which is significant between plasma insulin and plasma cholesterol, plasma LDL in studied groups but statistically significant negative correlation with plasma HDL as shown in Figs. (8-10).

Table (3): Levels of total cholesterol, triglycerides, HDL and LDL in studied groups.

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (Group 1) Mean±SD</th>
<th>High fat diet group (Group 2) Mean±SD</th>
<th>High fructose group (Group 3) Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC mg/dl</td>
<td>127.84±4.54</td>
<td>152.49±16.65*</td>
<td>138.12±9.53$</td>
</tr>
<tr>
<td>TG mg/dl</td>
<td>56.11±3.37</td>
<td>80.60±6.34*</td>
<td>70.58±7.43*</td>
</tr>
<tr>
<td>HDL mg/dl</td>
<td>51.44±5.098</td>
<td>36.35±5.45*</td>
<td>38.53±4.948*</td>
</tr>
<tr>
<td>LDL mg/dl</td>
<td>64.98±8.97</td>
<td>100.02±17.81*</td>
<td>85.47±10.444*</td>
</tr>
</tbody>
</table>

* Significant p as compared to control group (Group 1) ($p<0.001$).  
$ Non Significant p as compared to high fat diet group (Group 2) ($p>0.05$).

As regarding the mean values of total cholesterol, triglycerides, HDL and LDL levels in high fat diet group there was highly significant increase ($p$-value $<0.0001$ as compared with the mean values of the control group. There was also highly significant increase of high fructose intake values with control group as shown in Table (3). On the other hand the comparison of mean values between (Group 2) and (Group 3) as Shown in Table (4) and Figs. (4-7) non significant change with cholesterol and HDL and significant with TG and LDL.

There is positive correlation which is significant between plasma insulin and plasma cholesterol, plasma LDL in studied groups but statistically significant negative correlation with plasma HDL as shown in Figs. (8-10).

Table (4): Comparison of plasma levels of total cholesterol, triglycerides, HDL and LDL between high fat diet group (Group 2) and high fructose concentration group (Group 3).

<table>
<thead>
<tr>
<th>Item</th>
<th>High fat diet group (Group 2) Mean±SD</th>
<th>High fat fructose group (Group 3) Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC mg/dl</td>
<td>152.49±16.65</td>
<td>138.12±9.53$</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>TG mg/dl</td>
<td>80.60±6.34</td>
<td>70.58±7.43$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL mg/dl</td>
<td>36.35±5.45</td>
<td>38.53±4.948*$</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LDL mg/dl</td>
<td>100.02±17.81</td>
<td>85.47±10.444$</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Significant p as compared to high fat diet group (Group 1) ($p<0.001$).  
$ Non Significant p as compared to high fat diet group (Group 2) ($p>0.05$).
It can be noted that there was significant reduction of GLp-1 level in high fat diet group (Group 2) and high fructose concentration in drinking water group (Group 3) when compared to control group ($p$-value $<$0.001) Table (5). Comparison between high fat diet and high fructose groups revealed significant decrease in high fat diet (Group 2) than high fructose group (Group 3) ($p$<0.05).
There is negative correlation which is significant between GLP-1 with HOMA test, as shown in Fig. (12).

Table (5): Levels of GLP-1 in studied groups.

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (Group 1) Mean±SD</th>
<th>High fat diet group (Group 2) Mean±SD</th>
<th>High fructose concentration group (Group 3) Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 pmol/l</td>
<td>7.88±1.77</td>
<td>12.40±3.69*</td>
<td>17.49±0.65</td>
</tr>
</tbody>
</table>

* Significant \( p \) as compared to control group (Group 1) \((p<0.001)\).
+ Significant \( p \) as compared to high fat diet group (Group 2) \((p<0.001)\).

Table (6): Comparison of plasma levels of GLP-1 between high fat diet group (group 2) and high fructose concentration group (group 3).

<table>
<thead>
<tr>
<th>Item</th>
<th>High fat diet group (Group 2) Mean±SD</th>
<th>High fructose concentration group (Group 3) Mean±SD</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 pmol/l</td>
<td>7.88±1.77</td>
<td>12.40±3.69*</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

+ Significant \( p \) as compared to high fat diet group (Group 2) \((p<0.001)\).

Table (7): Levels of blood pressure in studied groups.

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (Group 1) Mean±SD</th>
<th>High fat diet group (Group 2) Mean±SD</th>
<th>High fructose concentration group (Group 3) Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>133.30±5.54</td>
<td>165.30±12.61*</td>
<td>169.80±18.87$</td>
</tr>
</tbody>
</table>

* Significant \( p \) as compared to control group (Group 1) \((p<0.001)\).
$ Non Significant \( p \) as compared to high fat diet group (Group 2) \((p>0.05)\).

Table (8): Comparison of levels of blood pressure between high fat diet group (group 2) and high fructose concentration group (group 3).

<table>
<thead>
<tr>
<th>Item</th>
<th>High fat diet group (Group 2) Mean±SD</th>
<th>High fructose concentration group (Group 3) Mean±SD</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure</td>
<td>165.30±12.61</td>
<td>169.80±18.87$</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

$ Non Significant \( p \) as compared to high fat diet group (Group 2) \((p>0.05)\).

Fig. (11): Comparison of levels of GLP1 in studied groups.

* Significant \( p \) as compared to control group (Group 1) \((p<0.001)\).
+ Significant \( p \) as compared to high fat diet group (Group 2) \((p<0.001)\).

Fig. (12): Negative correlation between GLP1 and HOMA.

* Significant \( p \) as compared to control group (Group 1) \((p<0.001)\).
+ Significant \( p \) as compared to high fat diet group (Group 2) \((p<0.001)\).

Regarding the levels of systolic blood pressure of rats in studied group reflected the effect of insulin resistance on blood pressure. Tables (7,8) Fig. (13) revealed that there was significant increase in systolic blood pressure in a high fat diet group (Group 2) and high fructose concentration in drinking water group (Group 3) compared to mean value of control group \((p\)-value <0.001\). These results indicated that insulin resistance is usually associated with hypertension. Also, comparison between high fat diet group and high fructose in drinking water group revealed non significant variation as shown in Table (8) and Fig. (13).

Fig. (13): Comparison of levels of blood pressure in studied groups.

* Significant \( p \) as compared to control group (Group 1) \((p<0.001)\).
$ Non Significant \( p \) as compared to high fat diet group (Group 2) \((p>0.05)\).
Discussion

The coincidence of obesity, insulin resistance, hypertension and dyslipidemia is commonly referred to as the ‘metabolic syndrome’. This condition affects approximately 20-40% of the population in the industrialized nations. Central obesity and alterations of adipokine secretion, together with a concomitant fat accumulation in different metabolically active tissues such as liver, muscle and pancreas, build the pathophysiologic basis of the metabolic syndrome. Hepatic steatosis is now often ed to the classical components mentioned above.

This study was undertaken to clarify the relation of both high fat diet, high fructose intake to induce of insulin resistance as well as hypertension. Another important target is to reveal the effect of insulin resistance on plasma GLP-1 level. There is no basal fasting GLP1 levels as it is rapidly destroyed by DPP IV. The results of the present study demonstrated that both high fat diet and high fructose intake cause insulin resistance with hyperglycemia, hyperinsulineamia, hyperlipidemia and hypertension. It also reveals that insulin resistance causes reduction in plasma GLP-1 level.

These results were in accordance with Jong et al. who reported that when male Sprague-Dawley rats consumed high-fat diets glucose tolerance is reduced, fasting plasma insulin was increased in animals fed saturated fat compared with chow-fed animals. Also, these results are in agreement with those reported by Michael et al. who found that blood glucose and plasma insulin levels were greater in fasted and non fasted mice fed a HFD 60% for 9 days than in mice fed control diet, but free fatty acids levels were similar in control group and HFD-fed mice.

The development of entire spectrum of the metabolic syndrome, including insulin resistance, visceral obesity and dyslipidemia because of high-fat diet, are reported due to activation of the function of the hypothalamus-pituitary-adrenal axis (HPA). Frequently evoked HPA-axis secretes excessive amount of cortisol. There are several studies which suggest that frequent stress or perturbed secretion of cortisol has a role in the development of visceral obesity, insulin resistance and its pathologies. Glucocorticoids bring about their multiple effects by activating the intracellular glucocorticoids receptor that binds to specific glucocorticoids-responsive elements in the vicinity of regulated genes and subsequently affect their expression. It is estimated that glucocorticoid receptors can interact as transcription factors as many as 30% of genes, so it is not surprising that glucocorticoids induce a wide range of response. Glucocorticoids oppose the insulin-mediated inhibition of hepatic glucose release [i.e. stimulate gluconeogenesis] and decrease glucose use in muscle.

Another mechanism that has been suggested to explain the insulin resistance of muscle glucose transport that develops with fat feeding and obesity is a change in the lipid composition of the plasma membrane. This seemed a reasonable possibility, as membrane lipid composition can affect the functioning of membrane-associated proteins, and two of the key proteins involved in the regulation of glucose transport, the glucose transporter and the insulin receptor, are constituents of the plasma membrane. There is considerable evidence that the catalytic activities of the glucose transporters and the binding properties of the insulin receptor are markedly sensitive to changes in the properties of the membrane lipid bilayer.

Concerning development of insulin resistance with high fructose intake in drinking water, these results are in agreement with Gerard D’Angelo et al. who performed their studies on male Sprague-Dawley rats, animals were divided into 2 groups: those that continued to receive the standard rat chow (control) and those switched to a high-fructose diet 66%. Animals maintained on the high-fructose diet exhibited modest but significant hyperglycemia, hyperinsulinemia, and hypertriglyceridemia compared with the control group.

The increased synthesis of triacylglycerol results primarily from both increases in the VLDL particle secretion rate by the liver and in VLDL particle size. Reductions in triacylglycerol clearance may be due in part to reductions in lipoprotein lipase activity using a fructose-fed Syrian golden hamster animal model.

The mechanisms potentially responsible for the overproduction of VLDL in the insulin-resistant state. They found evidence for enhanced lipoprotein assembly, reduced intracellular apolipoprotein B degradation, and increased expression of microsomal triacylglycerol transfer protein. Together, these findings help to explain the increased assembly and secretion of apolipoprotein-B-containing lipoprotein particles in a fructose-fed, insulin-resistant animal model. Chronic high fructose exposure seems to indirectly cause hyperinsulinemia and obesity through other mechanisms. One proposed mechanism involves glucose transporter 5
GLUT5), a fructose transporter that is found to have significantly higher expression levels in young Zucker obese rats compared to lean controls, implying a possible role of GLUT5 receptors in the pathology of metabolic syndrome associated with fructose feeding and insulin resistance [23]. In rats fed 66% fructose for 2 weeks, insulin receptor mRNA, and subsequent insulin receptor numbers in skeletal muscle and liver were significantly lower compared to rats fed a standard chow diet. Insulin resistance has also been correlated with intracellular TG stores, which are involved in lipotoxicity and beta cell failure leading to diabetes [24].

Concerning reduction of GLP1 with insulin resistance these results found that Insulin resistance was associated with impaired GIP and GLP-1 responses to a high fat & high fructose diet. The early GLP-1 response to food ingestion was impaired in insulin-resistant subjects. Thus the mean GLP-1 level among the insulin-resistant groups were $7.88 \pm 1.7$, $12.4 \pm 3.6$ pmol/l in a high fat & high fructose diet respectively, while the GLP-1 level in the control group $17.49 \pm 0.65$ pmol/l, $p < 0.01$.

Defective actions of the incretin hormones: Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), play significant roles in pathogenesis of T2DM [25]. These finding are consistent with results reported by Stonehouse et al., 2008 [26] who shown that the incretin hormones play an integral role in glucose homeostasis [27]. The observation that orally administered glucose provides a stronger insulinotropic stimulus than an intravenous glucose challenge, provide insight into the regulation of plasma glucose by the incretin hormones of healthy individuals. The incretin effect, as this is termed, may be responsible for 50% to 70% of the total insulin secreted following oral glucose intake [28].

Two different defects have been described. First, the insulinotropic activity of GIP is almost completely lost in patients with type 2 diabetes, whereas the efficacy of GLP-1 is preserved to a much greater extent. Secondly, it has been suggested that the secretion of GLP-1 might be impaired in patients with type 2 diabetes, whereas the majority of studies seem to agree that GIP secretion is rather normal in diabetic patient. GLP-1 levels was examined in different groups at high risk of developing type 2 diabetes, such as individuals with impaired glucose tolerance [29], women with a history of gestational diabetes, and first-degree relatives of patients with type 2 diabetes. However, the fact that GLP-1 levels were not impaired in any of these groups seems to refuse the hypothesis that impaired GLP-1 secretion is a primary defect in the pathogenesis of type 2 diabetes [30]. The alternative hypothesis is that impairments in GLP-1 concentrations develops secondary to other metabolic abnormalities in type 2 diabetes, such as hyperglycemia. Thus, whereas patients with longstanding type 2 diabetes and in relatively poor diabetic control appeared to have lower GLP-1 concentrations after oral glucose or meal ingestion, most studies examining patients with shorter diabetes duration and with only modest elevations of blood glucose concentrations did not find any defects in postprandial GLP-1 levels [29].

Although Vollmer et al., [31] provided evidence that acute elevations in blood glucose levels markedly reduce the concentrations of GIP and GLP-1 over a 4-h study period, the impact of chronic hyperglycemia on incretin release may well be different. Thus, it is conceivable that intestinal K and L cells partly adapt to the effects of high blood glucose levels or delayed gastric emptying to sustain a physiological incretin response.

Concerning development of hypertension with insulin resistance caused by HFD & HFD there were hypertension in both groups as compared to control fed rats. In addition, the rats fed HFD & HFD showed significant elevation in the basal plasma glucose, triglyceride, total cholesterol and insulin levels at the end of five weeks of dietary manipulation as compared to control group.

These results are in agreement with those reported by Thomas et al., 2007 [32] who found that Dogs fed a high-fat diet for 6 weeks exhibit many of the hemodynamic, neurohormonal, renal, and metabolic changes associated with obesity in human subjects, including weight gain, sodium retention, hypertension, tachycardia, hyperinsulinemia, insulin resistance, and activation of the sympathetic and renin-angiotensin systems. The blood glucose and plasma insulin levels were greater in fasted and non fasted mice fed a HFD 60% for 9 days than in mice fed control diet, but free fatty acids levels were similar in control group and HFD-fed mice [17]. These results also supported by those reported by Buettner et al., 2006 [33] who found that Free fatty acids (FFA) were increased in HFD with 1.3-fold elevation in HOMA values. Also plasma insulin showed increase when compared to control group.

Nevertheless, numerous studies using the fructose-fed rat have demonstrated that insulin resistance causes pronounced vascular dysfunction, including increased vasoconstrictor sensitivity,
suppressed endothelium-dependent relaxation and potassium channel function, and increased vascular superoxide production [34,35].

The mechanism of fructose-induced hypertension may be related to some factors as uric acid production, hyperinsulinemia, aldehyde formation and altered vascular reactivity have been implicated. Also long-term fructose feeding impaired vascular relaxation. Fructose feeding induced hypertension in normal-fed and high-salt-fed rats and was associated with an increased expression of the angiotensin II type 1 receptor in adipose tissue [36].

Conclusion:

It is concluded that consumption of excess fat, high fructose intake in diet, play a role in increasing incidence of insulin resistance, also we report evidence that the reduction of post-prandial plasma GLP-1 level in insulin resistant. These data suggest that GLP-1 is significant negatively correlated with HOMA test and the impaired incretin effect seen after a meal in patients with insulin resistance is caused, at least in part, by decreased secretion of GLP-1. Further investigation is also needed for the use of analogs of GLP-1 that are not susceptible to enzymatic degradation as Exenatide (Ex-4), (synthetic exendin-4) and the use of selective enzyme inhibitors to prevent in vivo degradation and enhance levels of the intact, biologically active enzyme inhibitors to dipeptidyl-peptidase-IV (DPP IV) inhibitors as a line for treatment of type 2 diabetes mellitus.

References

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