Is the Effect of Caloric Restriction on Type 2 Diabetes Mellitus in Rats Mediated Via Sirtuin-1?

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Abstract

Background: Type 2 diabetes mellitus is a long-lasting disease that can be improved but not cured. Insulin resistance is the initial disorder occurring in type 2 diabetes mellitus even before the development of hyperglycemia. Both insulin resistance and β-cell dysfunction are linked with obesity especially the visceral adiposity.

It was reported that over-nutrition and aging, which are the chief precipitating factors for diabetes, are positively correlated with reduced sirtuin-1 (SIRT1) activity resulting in hyperglycemia and hyperlipidemia. Therefore, reestablishing the normal level and activity of SIRT-1 in type 2 diabetes mellitus (T2DM) may be a promising method of treating diabetes.

SIRT1 is induced in several tissues during CR and energy deprivation is the major activator of SIRT1 over expression which will respond via stimulating lipolysis through increasing the expression of triglyceride lipase. SIRT1 also inhibits lipogenesis.

Aim of the Work: Is to assess the impact of caloric restriction on SIRT1 in the liver and pancreas of type 2 diabetic rats.

Material and Methods: 32 male albino rats were included in the study and divided into group I: Control group, group II: Diabetic group, group III: Pre-diabetes CR group and group IV: Post-diabetes CR group. After finishing the experimental study we measured the serum glucose level, serum insulin level, HOMA-IR, SIRT 1 level and activity in liver and pancreas of adult male rats.

Results: Our results revealed that both pre-diabetes CR and post-diabetes CR groups were associated with significant improvement of SIRT1 level and activity in liver and pancreas of T2DM rats in addition to their beneficial effect on improving the insulin sensitivity and thus reducing insulin resistance and concomitant hyperglycemia.

Conclusion: The decrease in SIRT1 associated with diabetes was actually attenuated by the 30% caloric restriction leading to significant improvement in T2DM.

Key Words: Type 2 diabetes mellitus – Caloric restriction – SIRT1 – Liver – Pancreas.

Introduction

DIABETES mellitus is a worldwide growing disease, mostly due to the increase in incidence of T2DM. Chronic diabetes results in diabetic vascular complications which are the main causes of morbidity and even death in these patients. Strict and maintained control of diabetes mellitus is complex even on multiple antidiabetic drugs. Therefore, the development of complementary treatments and novel prevention strategies for T2DM is urgent [1].

Mammals have 7 sirtuins that have NAD+ dependent deacetylase activity [2]. So, their activity is related to the energy state of the cell. Sirtuins are known as important regulators of nutrient utilization and energy metabolism [3].

SIRT1 has been shown to be a major regulator for pancreatic insulin secretion, which sequentially triggers glucose uptake and utilization [4]. Also, in the liver, SIRT1 has affect gluconeogenesis and fat metabolism [5].

Deng [6] showed that caloric restriction notably improves the sensitivity to insulin and markedly increases gene expression of SIRT1 while decreasing the apoptosis ratio of pancreatic β-cells in diabetic rats.

The present work aimed to study the possible preventive or curative effect of 30% caloric restriction mediated via SIRT1 in type 2 diabetic rats.

Material and Methods

32 adult male rats of local strain weighing 150-200 grams were used in the study. Animals were fed with standard laboratory chow and water...
“ad libitum” and housed in animal house unit of Faculty of Medicine, Cairo University, at normal room temperature; animals were acclimatized to these conditions for 10 days before the experiment. This study was done during 2014.

Animals were housed in groups of 8 each in identical wire-bottomed cages and were divided into four groups: Control group: Rats in this group were assigned to a freely eating (ad libitum) and kept sedentary till the end of the experiment, Diabetic group: We induced diabetes using intraperitoneal injection of a single dose of Streptozotocin 40mg/kg [7] without any nutritional modification till the end of the study, pre-diabetes CR group: As the food intake of the freely eating rats was measured every other day, and the CR rats were given food equal to 70% of the average amount of food eaten by the freely eating controls for one month then we induced diabetes later on [8] and post-diabetes CR group: Eight diabetic rats were given food equal to 70% of the average amount of food eaten by the freely eating controls for one month post diabetes.

At the end of the study protocol, fasting blood samples were withdrawn retro-orbital using a capillary tube for assessment of fasting serum glucose, fasting serum insulin and HOMA-IR. Afterward, animals were scarificed followed by rapid excision of liver and pancreas for further assessment of SIRT1 level and activity.

**Determination of serum glucose level:** Oxidation of glucose under the influence of glucose oxidase to gluconic acid, and hydrogen peroxide is produced. The hydrogen peroxide acts on amino-4-antipyrine in the presence of phenol, giving rise to a colored complex (quinoneimine) which can be determined colorimetrically. Then, the absorbance of the standard and the samples were measured spectrophotometrically against blank at 500 nanometer light wave length [9].

**Determination of the serum insulin level:** Using the rat insulin ELISA kits, it is based on the direct sandwich technique in which two monoclonal antibodies are directed against separate antigenic determinants on the insulin molecule. During incubation, insulin in the sample reacts with peroxidase conjugated anti-insulin antibodies and anti-insulin antibodies bound to the micro titer wells. A simple washing step removes unbound enzyme labeled antibody. The bound conjugate is detected by reaction with 3, 3’, 5, 5’-tetramethylbenzidine. The reaction is stopped by adding acid to give a colorimetric end point result that is read spectrophotometrically. The absorbance was measured at 450nm [10].

**Calculation of homeostasis model assessment insulin resistance index (HOMA-IR):** HOMA-IR index was calculated as the product of fasting serum insulin ([IU/L] and fasting serum glucose (mmol/L) divided by 22.5: When the result is greater than 4.0 it is an indicator of insulin resistance [11].

**Determination of SIRT1 activity:** SIRT1 activity fluorometric assay kit measures the activity of SIRT1 by the basic principle of changing a SIRT1 reaction into the activity of the protease. In order to measure the enzyme activity of SIRT1, which is the NAD+ dependent histone deacetylase, and its homolog, this kit is designed so that the activity of NAD+ dependent histone deacetylase can be measured under existence of Trichostatin A, which is the powerful inhibitor of HDACs [12].

Detection of SIRT1 gene expression by Real time-Polymerase Chain Reaction (real-time-PCR) in liver and pancreas: RNA isolation and reverse transcription: RNA was extracted from the hepatic and pancreatic tissues homogenate using the RNeasy plus mini kit (Qiagen, Venlo, The Netherlands), according to the manufacturer’s instructions. Genomic DNA was eliminated by a DNase-on-column treatment supplied with the kit. The RNA concentration was determined spectrophotometrically at 260nm using the Nano Drop ND-1000 spectrophotometer (Thermo Fisher scientific, Waltham, USA) and RNA purity was checked by means of the absorbance ratio at 260/280nm. RNA integrity was assessed by electrophoresis on 2% agarose gels. (1 µl) of RNA were used in the subsequent cDNA synthesis reaction, which was performed using the reverse transcription system (Promega, Leiden, The Netherlands). Total RNA was incubated at 70°C for 10min to prevent secondary structures. The RNA was supplemented with MgCl2 (25mM), RTase buffer (10X), dNTP mixture (1.0mM), oligo (t) primers, RNase inhibitor (20U) and AMV reverse transcriptase (20U/µl). This mixture was incubated at 42°C for 1h [13].

**Quantitative real time PCR:** QPCR was performed in an optical 96-well plate with an ABI PRISM 7500 fast sequence detection system (Applied Biosystems, Carlsbad, California) and universal cycling conditions min 95°C, 40 cycles of 15s at 95°C and 60s at 60°C). Each 10 µl reaction contained 5 µl SYBR Green Master Mix (Applied Biosystems), 0.3 µl gene-specific forward and reverse primers (10 µM) 2.5 µl cDNA and 1.9 µl nuclease-free water. The sequences of PCR primer
pairs used for each gene are shown in (Table 1). Data were analyzed with the ABI prism sequence detection system software and quantified using the v1.7 sequence detection software from PE Biosystems (Foster City, CA). Relative expression of studied genes was calculated using the comparative threshold cycle method. All values were normalized to the GAPDH genes [13].

Table (1): Primer sequences used for RT-PCR [13].

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRT1</td>
<td>F: 5’-CATGAGCTGCACTGATGT-3’, R: 5’- GAGCCTGCCCGTCAACTAGG-3’;</td>
</tr>
<tr>
<td>GAPDH</td>
<td>F: 5’-ATGAGGCCCCAGGCTCTCCAT-3’, R: 5’-CCAGGCGAGCCACATCGCTC-3’</td>
</tr>
</tbody>
</table>

Data were tabulated and analyzed by SPSS (statistical package for the social science software) using the statistical package version 15. Quantitative data were expressed using mean ± standard deviation for the variables. The data from control and test groups were compared using analysis of variance (ANOVA) and multiple comparisons (Post Hoc test) for the quantitative variables. Probability values of less than 0.05 were considered as statistically significant [14].

Results

Comparison between serum glucose (mmol/L), serum insulin (IU/L), levels and HOM-IR in all studied groups:

Our results revealed that: Compared to control group as observed in (Table 2) the fasting serum levels of glucose and insulin (IU/L) and concomitantly HOMA-IR were significantly elevated (p = 0.000) in diabetic group. Mean values in diabetic group were respectively 12.81 ± 1.94; 17.88 ± 1.23 and 10.34 ± 2.17 versus 4.87 ± 0.18; 9.98 ± 1.24 and 2.16 ± 0.24 in control group.

Moreover, Table (1) reflected that both pre diabetics and post diabetes 30% CR groups achieved significant reduction (p<0.000) in the levels of glucose, insulin and accordingly HOMA-IR relative to diabetic group with mean values of 6.57 ± 2.21; 12.80 ± 1.20 and 3.82 ± 1.62 respectively in pre-diabetes CR group; 6.51 ± 1.31; 10.74 ± 1.69 and 3.18 ± 1.16 respectively in post-diabetes CR group, 12.81 ± 1.94; 17.88 ± 1.23; and 10.34 ± 2.17 respectively in diabetic group. Notably, post-diabetes CR nearly normalized each of serum glucose, insulin levels and HOMA-IR relative to control group achieving mean values of 6.51 ± 1.31; 10.74 ± 1.69 and 3.18 ± 1.16 respectively versus 4.87 ± 0.18; 9.98 ± 1.24 and 2.16 ± 0.24 respectively in control group.

Although the glucose level and HOMA values were insignificantly higher in pre-diabetes CR group, relative to control group (p>0.05) but the serum insulin level (IU/L) was significantly higher (p=0.012). Mean values of glucose, insulin and HOMA-IR were respectively 6.57 ± 2.21; 12.80 ± 1.20 and 3.82 ± 1.62 in pre-diabetes CR group versus 4.87 ± 0.18; 9.98 ± 1.24 and 2.16 ± 0.24 in control group.

Comparison between the SIRT1 level and SIRT1 activity (ng/dl) in the liver and pancreas of all studied groups:

As shown in Table (3), SIRT1 level and activity in the liver were significantly (p=0.000) decreased following induction of diabetes. Mean values were 0.98 ± 0.22 and 2.28 ± 0.58 in group II versus 2.17 ± 0.35 and 5.16 ± 1.28 in GpI respectively. Also, SIRT1 level and activity in pancreas were significantly decreased (p=0.000) achieving mean values of 0.70 ± 0.25 and 2.99 ± 1.13 in GpII versus 1.72 ± 0.55 and 8.24 ± 1.13 in GpI respectively.

Table (3) and Figs. (4-7) showed that pre-diabetes CR group revealed a significant improvement (p=0.000) in SIRT1 activity (ng/dl) in liver, SIRT1 level (ng/dl) and activity in the pancreas relative to diabetic group. However, SIRT1 level in liver was insignificantly increased (p>0.05) in pre-diabetes CR group compared to diabetic group.

Additionally, relative to control group, SIRT1 activity in liver and SIRT1 level in pancreas in pre-diabetes CR group showed insignificant difference (p>0.05); but SIRT1 level in liver (p=0.000) and SIRT1 activity in pancreas (p=0.045) still exhibited a significant difference. Mean values of SIRT1 level and activity in liver were respectively 1.38 ± 0.32; 5.81 ± 1.46 in pre-diabetes CR group versus 0.98 ± 0.22; 2.28 ± 0.58 in diabetic group and 2.17 ± 0.35; 5.16 ± 1.28 in control group while in pancreas they were respectively 1.87 ± 0.33; 6.12 ± 1.10 in pre-diabetes CR group versus 0.70 ± 0.25; 2.99 ± 1.13 in diabetic group and 1.72 ± 0.55; 8.24 ± 1.13 in control group.

Also, post-diabetes caloric restriction was significantly helpful in reversing the diabetes associated reduction in the level and activity of SIRT1 in liver and pancreas. Data in Table (3) showed a significant increase (p=0.000) in SIRT1 level and activity in the liver of post-diabetes CR group relative to diabetic group, but with insignificant difference (p>0.05) compared to control group. Mean values were respectively 1.73 ± 0.29; 6.22 ± 1.22 in post-diabetes CR group versus 0.98 ± 0.22; 2.28 ± 0.58 in diabetic group and 2.17 ± 0.35; 5.16 ± 1.28 in control group.
Regarding SIRT1 level and activity (ng/dl) in pancreas, post-diabetes CR group results showed significantly (p=0.000) higher values compared to diabetic group, even with no significant difference relative to control group (p>0.05). Mean values were respectively 2.17±0.50; 7.99±0.67 in post-diabetes CR group versus 0.7±0.25; 2.99±1.13 in diabetic group and 1.72±0.55; 8.24±1.13 in control group.

Also, our results in Table (3) recorded no significant difference when comparing between the effects of caloric restriction either before or after induction of diabetes on SIRT1 level and activity in the liver and pancreas (p>0.05). Mean values for SIRT1 level and activity in the liver were respectively 1.73±0.29 and 6.22±1.22 in post-diabetes CR group versus 1.38±0.32 and 5.81±1.46 in pre-diabetes CR group. Mean values of SIRT1 level and activity in pancreas were respectively 2.17±0.50 and 7.99±0.67 in post-diabetes CR versus 1.87±0.33 and 6.12±1.10 in pre-diabetes CR group.

Table (2): Changes in fasting serum glucose (mmol/L), fasting serum insulin (μIU/L) levels and HOMA-IR in all studied groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>Diabetic group</th>
<th>Pre-diabetes CR group</th>
<th>Post-diabetes CR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.87±0.18</td>
<td>12.81*±1.94</td>
<td>6.57*±2.21</td>
<td>6.51*±1.31</td>
</tr>
<tr>
<td>Insulin (μIU/L)</td>
<td>9.98±1.24</td>
<td>17.88*±1.23</td>
<td>12.80*±1.20</td>
<td>10.74*±1.69</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.16±0.24</td>
<td>10.34*±2.17</td>
<td>3.82*±1.62</td>
<td>3.18*±1.16</td>
</tr>
</tbody>
</table>

Values are represented as mean ± SD.
*: Significant change comparing corresponding values to diabetic group.
**: Significant change comparing corresponding values to control group.

Concerning the serum insulin level, it did not show any significant relationship with the level and activity of SIRT1 in the pancreas although it was significantly decreased concomitant with the rise in SIRT1 level and activity in the liver.

Table (3): Changes of SIRT1 level (ng/dl) and SIRT1 activity (ng/dl) in liver and pancreas in all studied groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>Diabetic group</th>
<th>Pre-diabetes CR group</th>
<th>Post-diabetes CR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRT1 level</td>
<td>2.17±0.35</td>
<td>0.98*±0.22</td>
<td>1.38*±1.46</td>
<td>1.73*±0.29</td>
</tr>
<tr>
<td>(liver)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>SIRT1 activity</td>
<td>5.16±1.28</td>
<td>2.28*±0.58</td>
<td>5.81*±1.46</td>
<td>6.22*±1.22</td>
</tr>
<tr>
<td>(liver)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRT1 level</td>
<td>1.72±0.55</td>
<td>0.70*±0.25</td>
<td>1.87*±1.33</td>
<td>2.17*±0.33</td>
</tr>
<tr>
<td>(pancreas)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRT1 activity</td>
<td>8.24±1.13</td>
<td>2.99*±1.13</td>
<td>6.12*±1.10</td>
<td>7.99*±0.67</td>
</tr>
<tr>
<td>(pancreas)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Values are represented as mean ± SD.
*: Significant change comparing corresponding values to diabetic group.
**: Significant change comparing corresponding values to control group.

Fig. (1): Changes in serum glucose level in all studied groups.
Fig. (2): Changes in serum insulin level in all studied groups.

Values are represented as mean ± SD.
*: Statistically significant compared to control group (p<0.05).
**: Statistically significant compared to diabetic group (p<0.05).
Fig. (3): Changes in HOMA-IR value in all studied groups. Values are represented as mean ± SD.
*: Statistically significant compared to control group (p<0.05).
**: Statistically significant compared to diabetic group (p<0.05).

Fig. (4): Changes in SIRT1 level (liver) in all studied groups. Values are represented as mean ± SD.
*: Statistically significant compared to corresponding value in control group (p<0.05).
**: Statistically significant compared to corresponding value in diabetic group (p<0.05).

Fig. (5): Changes in SIRT1 activity (liver) in studied groups. Values are represented as mean ± SD.
*: Statistically significant compared to corresponding value in control group (p<0.05).
**: Statistically significant compared to corresponding value in diabetic group (p<0.05).

Fig. (6): Changes in SIRT1 level (pancreas) in all studied groups. Values are represented as mean ± SD.
*: Statistically significant compared to corresponding value in control group (p<0.05).
**: Statistically significant compared to corresponding value in diabetic group (p<0.05).

Fig. (7): Changes in SIRT1 activity (pancreas) in all studied groups. Values are represented as mean ± SD.
*: Statistically significant compared to corresponding value in control group (p<0.05).
**: Statistically significant compared to corresponding value in diabetic group (p<0.05).

Discussion

Development of insulin resistance has been linked to obesity that will contribute to the development of type 2 diabetes mellitus [15]. The role of diet, irrespective of degree of obesity, in modulating insulin resistance remains uncertain but obviously lowered blood glucose levels [16].

SIRT1 was initially recognized as a regulator of gluconeogenic gene expression and lipid metabolism [17]. SIRT1 was documented to be involved in insulin signaling in insulin-sensitive organs [18]. In addition, SIRT1 adjusts insulin secretion, adiponectin production, gluconeogenesis, inflammation, and oxidative stress, which collectively participate in the development of IR [19].

These data show that caloric restriction notably improves the sensitivity to insulin and considerably
raises the protein expression of SIRT1 while decreasing the pancreatic apoptosis in type 2 diabetic rats [1].

The present work has been designed to investigate the possible influence of caloric restriction on SIRT1 in diabetic rats and if CR could be a line of treatment as it is helpful in re-establishing the physiological relevant activity of SIRT1 known to be attenuated with diabetes. We also tried to test if it has any preventive value through tempering of SIRT1 disorders associated with the development of T2DM.

Therefore, we induced type 2 diabetes in eight adult male rats (diabetic group) by single intraperitoneal injection of 40mg/kg streptozotocin, a toxin producing incomplete pancreatic P-cell apoptosis [14].

Subsequently, significant hyperglycemia was developed in diabetic group relative to control rats. Additionally, diabetic rats exhibited significant hyperinsulinemia concomitant with development of significant insulin resistance (increase HOMA-IR) settling the typical features of type 2 diabetes mellitus.

Our results were in agreement with Burant et al., [20] who suggested that peripheral insulin resistance accompanying the streptozotocin induced DM, may be due to either alterations in insulin receptor structure or glucose transporters, resulting in defective insulin signaling.

As Caton et al., [17] demonstrated that SIRT1 is concerned with the regulation of glucose homeostasis and insulin sensitivity we thought that studying the SIRT1 disorders associated with diabetes might be beneficial. Our results showed that SIRT1 level and activity were decreased significantly in the liver and the pancreas of diabetic rats.

Our results were in agreement with Suvarna., [3] who found that the nutrients availability such as high serum glucose in diabetic rats are associated with decreased levels of NAD/NADH + which are the main stimulators of SIRT1 -- leading to decreased SIRT1 release and activity.

However, we could not specify if the decrease in SIRT1 shared partially in the development of insulin resistance and subsequent hyperglycemia or the streptozotocin-induced type 2 diabetes was the initial cause of the observed decrease in SIRT1.

However, our results in diabetic group revealed that the elevated serum glucose, insulin and HOMA-IR were parallel to the decline in SIRT1 level and activity (inverse correlation).

Data could be explained by Sebastián et al., [21] who suggested that nutrients overabundance, sedentariness and genetics interact to produce a state of metabolic vulnerability that leads to abnormal regulation of SIRT1 resulting in insulin resistance and lipid metabolism disorders.

Wang et al., [22] showed that hepatic knockout of SIRT1, leads to hepatic glucose overproduction and the resulting increase in reactive oxygen species distorts insulin signaling in the adipose tissues and muscles causing insulin resistance.

In addition, Bordone et al., [23] showed that insulin secretion from pancreatic P-cells was decreased following the reduction in SIRT1 levels. This fact was explained by Rogina and Helfand., [24] who noticed elevated levels of UCP2 in cells with reduced SIRT1. Thus ATP synthesis was reduced lowering the amplitude of insulin induction by glucose.

Archer., [25] reported that caloric restriction has significant ameliorating effect on both serum glucose and insulin levels in pre-diabetics and diabetics even those with complications. Consistent with this, in the present work, the reduction of caloric intake by 30% for a period of one month before induction of diabetes in rats achieved a significant increase in insulin sensitivity which was proved by the decrease in insulin resistance (HOMA-IR) and consequently the fasting glucose level relative to diabetic group.

Our results were in agreement with Ohneda et al., [26] who documented that CR for 3 months prohibited the reduction of P-cell GLUT-2 and P-cell volume and preserved the stimulatory effect of glucose on insulin secretion.

In addition, Manjer et al., [27] reported that the serum glucose level was completely normalized in 50% of study members with initial IGT and those with early-stage T2DM after following lifestyle modification only, after a mean follow-up of 6 years.

In addition to the beneficial effect of CR on serum glucose and insulin, our work showed a significant improvement in SIRT1 level and activity in liver and SIRT1 level and activity in pancreas of pre-diabetes CR group relative to diabetic rats.

Our results were in agreement with Gillum et al., [28] who found that moderately and severely
obese rats exhibited significant reductions in SIRT1 mRNA expression which were elevated markedly after CR.

Similarly, Bertoni et al., [29] reported that CR increases the levels of SIRT1 in the liver and muscle, which are basic insulin-sensitive organs. In white adipose tissues, SIRT1 was shown to impede adipogenesis and to diminish fat storage [30]. Moreover, SIRT1 knockout mice are unresponsive to the metabolic actions of caloric restriction [31].

Crujeiras et al., [32] reported that CR induces the endothelial nitric oxide synthase (eNOS) resulting in excessive NO production. Interestingly, SIRT1 gene is triggered by NO.

SIRT 1 is an important regulator of the mammalian metabolic response to CR [33] which was observed to some extent, in our results when the significant rise in SIRT1 in pre-diabetes CR group was significantly related to the decrease in serum glucose, insulin and HOMA-IR.

In support of our results, Liu et al., [34] demonstrated that upon six hours fasting, SIRT1 deacetylated CRTC2 and so suppressed gluconeogenesis.

As we demonstrated the beneficial effect of pre diabetes CR, we also tried to speculate the possible valuable role of CR in diabetic rats. Our results revealed that fasting serum glucose level, fasting serum insulin level and HOMA-IR were significantly decreased after 30% CR for 1 month in diabetic rats compared to diabetic group.

In support of these findings, Andreelli et al., [35] reported that the expression of p85 PI3K which is the main mediator of insulin signaling was improved during CR in skeletal muscle of diabetics.

Additionally, the 30% CR after induction of diabetes was significantly helpful in reversing diabetes associated reduction in the level and activity of SIRT1 in both liver and pancreas. Our values showed a significant increase in SIRT1 level and activity in post-diabetes CR group relative to diabetic group. Also, SIRT1 level and activity in pancreas, achieved a significantly higher value in post-diabetes CR group than diabetic group with full improvement of the pancreatic tissues.

Our results were in agreement with, Deng et al., [1] who found that as a result of 60% CR in model of T2DM rats with a low-dose of STZ for 1 month, the mRNA and protein expression of SIRT1 in islet beta cells significantly increased; beside, the apoptosis ratio of islet beta cells in diabetic rats decreased remarkably. Oppositely, Chen et al., [36] concluded that SIRT1 protein levels and activity decrease in the CR liver. The highly fed liver is concomitant with a high NAD/ NADH ratio, while a low ratio was observed in the CR liver.

Moreover, the significant improvement of SIRT1 in post-diabetes CR group was significantly associated with significant improvement in serum glucose, insulin levels and HOMA but further work is still needed to demonstrate if these parameters are directly or indirectly interrelated.

In conclusion, both pre-diabetes CR and post-diabetes CR regimens were associated with significant improvement of insulin resistance and its subsequent hyperglycemia beside their role in attenuation of the marked decrease of SIRT1 in the liver and pancreas that accompanied the induction of type 2 diabetes mellitus.

Based on the findings of this study, we recommend for further work and research to explore the definite mechanisms linking CR and SIRT1 and to evaluate their beneficial roles in humans.

References


ان داء السكري من النوع الثاني هو مرض طويل الأمد يمكن تحديبه ولكن لا يمكن الشفاء منه. وتشمل مقاومة الأنسولين في الاضطراب الأولي الذي يحدث في النوع الثاني من داء السكري حتى قبل ارتفاع مستوي السكر في الدم. كما يوجد ارتباط بين كل من مقاومة الأنسولين وضغط خلايا بيتا مع السمنة وخاصة سمنة الاحشاء.

والجدير بالذكر أن الإفرات في التغذية والشيوعة، والذين يعتبران من العوامل الرئيسية المسببة لمرض السكري، يرتبطان بشكل إيجابي مع انخفاض مستوى سونتوين-1 (سرت-1) مما يؤدي إلى ارتفاع السكر الدهون في الدم. وذلك، فإن إعادة سرت-1 لمستواه ونشاطه الطبيعي في النوع الثاني من داء السكري قد يكون وسيلة واعدة لعلاج هذا المرض.

إن الحد من السعرات الحرارية والحرمان من الطاقة هما المنطرين الرئيسيان لتصنيع سرت-1 في العديد من الأنسجة والذين سيقدمان بتحفيز تكسير الدهون عن طريق تشغيل انزيمي السمنة عمن تكسير الدهون الثلاثية كما يمكن عملية تصنيع الدهون أيضا.

إن الدراسة الحالية تهدف إلى تقييم تأثير الحد من السعرات الحرارية على سرت-1 في الكبد والبنكرياس في الجرذان المصابة بالنداء الثاني من داء السكري.

وأجريت هذه الدراسة على 23 جرذًا من الجرذان الابيض البالغة وتم تقسيمهم إلى: المجموعة الضابطة، مجموعة مرضى السكري، مجموعة الهدف من السعرات الحرارية ما قبل احداث السكري ومجموعة الهدف من السعرات الحرارية ما بعد أحداث السكري. وبعد الانتهاء من هذه الدراسة التجريبية فذك ريا قياس كل من مستوي الجلوتين والأنسولين في الدم مقاومة الأنسولين ومستوي ونظام سرت-1 في الكبد والبنكرياس.

وكشفت نتائجنا أن كلا من مجموعة الهدف من السعرات الحرارية ما قبل أحداث السكري ومجموعة الهدف من السعرات الحرارية ما بعد أحداث السكري قد أظهرت مهولا في مستوى ونشاط سرت-1 في الكبد والبنكرياس في الفئران المصابة بالنوع الثاني من داء السكري بالإضافة إلى تأثيرهم المفيد على تحسين حساسية الأنسولين وبالتالي تقليل مقاومة الأنسولين ومستوى السكر في الدم.

والخلاصة: إن الانخفاض في مستوى ونشاط سرت-1 المصباح لحدود داء السكري قد تحسن بشكل ملحوظ بعد الحد من السعرات الحرارية بنسبة 20%. 