Protective Effect of Melatonin on Glycemic Index and The Fat Mass Induced After High Fat Diet in Adult Male Rats

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Abstract
The present study was curried out to investigate the effect of obesogenic diet on glycemic index and fat both body weight, as well as fat accu/.mulation. . For this purpose, 30 adult rats were subjected and rodomly divided into three equal groups, Control groups (CC) animals in this group recieved control chew diet and, high fat diet group (HFD), rats in this group fed diet rich in fat, whereas, melatonin group (HFD+M), in this group the animals exposed to high fat diet with IP injection of 10 mg/kg body weight melatonin along the period. The results revealed a significant increase in the level of serum glycemic index, serum leptin and decrease body weight but increase fat mass during the experimental periods. To sum up, melatonin ameiolerates the effects of exposing rats to diet rich in fat and brings glycemic index and leptin hormone close to noemal values.

Keywords: High fat diet, Melatonin, Leptin, Glycemic index Body weight, Retroperetonial fat.

1. Introduction

Obesity and type 2 diabetes, as the fastest-growing diseases, have attracted worldwide attention. Over nutrition, high-fat diet and sedentary lifestyles are main risk factors for development and progression of type 2 diabetes [1]. Over energy in the form of lipid and glycogen is stored in muscle, fat and liver tissues [2,3]. However, extreme lipid accumulation in these tissues causes intracellular reactive oxygen species (ROS) generation and oxidative stress [4], resulting in abnormalities of glucose and lipid metabolism [2]. As is known to all, skeletal muscle, adipose tissue and liver are important organs to maintain blood-glucose homeostasis and energy supply in human and animals. Skeletal muscle absorbs above 70% postprandial blood glucose in response to insulin [5]. White adipose tissue (WAT) is the major organ responsible for lipid synthesis and storage [6]. Liver is responsible for glucose storage and synthesis, fatty acid synthesis, and lipid circulation [7]. High fat diet can lead to accumulation of fat mass and imbalance distribution of fat in the body [8]. Visceral fat tissue is considered a dynamic endocrine organ that produces adipokines such as leptin, the later adipokines have a crucial function in food intake, energy homeostasis, metabolism, insulin sensitivity and production, endothelial function and inflammation [9]. Obesity is a serious risk factor in so-called metabolic syndrome, specifically with visceral fat accumulation, which includes insulin resistance, glucose intolerance, hypertension, and dyslipidemia [10], diet high in fat can act on toll-like receptors on adipocytes leading to activation of the inflammatory cytokine and the production of reactive oxygen species [10]. Leptin correlated with body weight, plasma insulin and amount of intra-abdominal fat plasma leptin was increased by a high-fat diet, the reduction of plasma leptin was correlated with the reduction of plasma insulin [11]. Melatonin dialy administration effect on some physiological parameter such depress the plasma glucose and insulin level, the inhibitory role of melatonin either either on cholestrol absorbtion from gastric intestine tract or its synethesis from cell and melatonin increase conver of melatonin to bile acids [12,14]. Another effect of malatonin on body weight the malatonin reduction in waist cirumference and lowering obesity [13], melatonin supplementation therapy in young animals reduces the size of the visceral fat deposits.

Therefore, reducing oxidative stress in the tissues can reverse disorders of glucose-lipid metabolism to control and treat type 2 diabetes. The aims of this study is to determine the Protective effect of Melatonin on glycemic index and Body weight and some hormonal adipokines such as leptin induced by High Fat Diet in adult male Rats.

2. Materials and Methods

A 30-adult male rat were used, mean weight was (160-200) g, they were housed in special metal cages (15×70×60) cm in room in the animal house of veterinary medicine college, Baghdad university, under ethical approval. The animals were kept under observation ten day prior to the study for adaptation with free access for food and water.

The experimental animals divided randomly to three

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group according to experimetal desinge as following:

1. Control groups (CC), animals in this group fed normal diet as described in table (1-1) throughout the period of experiment and IP injection with normal saline.
2. High fat diet group (HFD), rats in this group were fed high fat diet as described in table (1-1) for 8 weeks with IP injection along the period of experiment.
3. Melatonin group (HFD+M), in this group the animals were fed saturated high fat diet for 8 weeks with IP injection of 10 mg/kg body weight melatonin along the period [14,15,16].

3. Preparation of the high fat diet

The high fat diet was made weekly and stored in a sealed bag, kept out of light, and stored at 4°C until used made it as pelleted form or as round, high-fat diet formulation and composition are shown in table (1-1)

Table 1-1 high fat diet formula (saturated animal fat) (17)

Ingredient	Normal diet (g/kg diet)	High fat diet (g/kg diet)
Corn starch	650	150
Casein	200	200
Tallow fat	0	400
oil	50	0
Sucrose	0	150
Cellulse	50	50
Vitamin mix	10	10
Methionine	3	3
salt	2	2

Body weight

The rat in all group weighting every week and measered by electic scale (CAMARY).

Retroperitoneal fat mass (Units % ratio)

Retroperitoneal fat content was determined post mortem by making a midline incision, moving the viscera and reproductive fat to one side, and cutting all retroperitoneal fat from the dorsal wall of the abdominal cavity and fat enveloping the kidneys. This was weighed and expressed as a percentage of whole-body mass.

Blood sampling

The Blood was collected by direct heart puncture after overnight fasting at end of two months, and after anesthetized of animal with Xylizen and ketamin hydrochloride injection, blood was placed in gel test tube and left to stand for 30 minutes at room temperature to allowing clotting. The serum samples were prepared by centrifugation at 3000 rpm for 10 minutes to estimate the levels of complement components serum glucose and serun insulin and serum leptin.

Parameters of study

1. Assessing the glucose levels in serum (mg/dl):
2. Using a specific glucose kit, the serum glucose concentration was determined enzymatically (through enzymatic oxidation) acording to (18).
3. Determination of serum Insulin concentration(µIU/ml):

Serum insulin concentration were determined using a rat insulin ELISA kit. according to company instruction Bioassay Technology Laboratory (BT-LAB)

Determination of Insulin Resistance:

Resistance to Insulin (IR) was assessed by using the homeostasis model assessment (HOMA) index, which is depend on concentration of serum glucose (FSG) and serum concentration (FSI) at fasting (19).

1- Assessment of Leptin hormone in male rat's serum:

Leptin concentration in male rat's serum (ng/ml) was measured by ELISA kit. according to company instruction Bioassay Technology Laboratory (BT-LAB)

4. Statistical Analysis

GraphPad Prism software version 9.1.0 was used to statistically analyzed the obtained data by Two-way and One-Way ANOVA. When ANOVA was significant, the data were post hoc tested Tukey's test. Data are as mean ± standard error (SE), while the number of animals represented by (n) statistically significant was accepted when ($P<0.05$).

5. Results

1- Effect of High Fat Diet and melatonin on serum Glycemic Index (Glucose, Insulin and Insulin Resistance).

1.1 Serum Glucose Concentration (mg/dl)

The serum glucose concentrations at the beginning of experiment (week zero) and at the end of experiment (week 8) is illustrated in table (1-2). The serum glucose concentrations were non-significantly differed ($P>0.05$) in all experimental groups at zero time when compared with each other, whereas at the 8 weeks of experiment the value of this parameter was significantly high ($P<0.05$) in the treated groups (HFD and HFD+M) compare with zero time in the same groups and compare with the CC group at 8 weeks. Despite of this increment in HFD+M, however, it still close to normal range. The effect of HFD was significantly obvious ($P<0.05$) on serum glucose concentrations at 8 weeks in HFD group with mean value (295.25±1.461) compare to the same group (84.625±2.500) at zero time; Administration of melatonin brings the glucose concentration close to normal in HFD+M group at 8 weeks when it compared with CC groups at 8 weeks Besides, numerical improvement in glucose concentration was observed in HFD+M group at 8 weeks with mean value (130±0.732) comparing with HFD group (295.25±1.461). There were significant differences ($P<0.05$) in control group at zero time (79.625±3.179) when it compared with same groups at 8 week (113.625± 1.238), however, still in the normal range.

Groups Time	CC	HFD	HFDM
Zero time	79.625± 3.179 Aa	84.625± 2.500 Aa	81.75± 2.297 Aa
8 Weeks	113.625± 1.238 Ab	295.25± 1.461 Bb	130.5± 0.732 Cb
Data represented as mean ± SEM, n = 8 each group. *Upper-case letters indicate the differences between groups in the same period of time. *Lower-case letters indicate the differences between. zero time vs 8 weeks of expewriment for the same group, .			

1.2. Serum Insulin level (µIU/ml)

In the current study, results of serum insulin show that there was a significant ($p<0.05$) increase in serum Insulin level in a group fed HFD (9.956±0.008) as compared with other groups at 8 weeks. Moreover, there was non-significant decrease ($p>0.05$) HFD+M group (5.982±0.006) and CC group (6.225±0.014) at the end of experiment. On the other hand, there was significant difference ($p<0.05$) in all groups at 8 weeks when they compared with the insulin levels at the beginning of study. This differences are significant ($p<0.05$), whereas the highest significant were values was in HFD group at 8week vs. week zero with value (9.956±0.008),(4.784± 0.180), respectively, As shown in and the table (1.3).

Groups Time	CC	HFD	HFDM
Zero time	4.78± 0.180 Aa	4.784± 0.180 Aa	4.974± 0.179 Aa
8 Weeks	6.225± 0.014 Ab	9.956± 0.008 Bb	5.982± 0.006 Cb
Data represented as mean ± SEM, n = 8 each group. *Upper-case letters indicate the differences between groups in the same period of time. *Lower-case letters indicate the differences between. zero time vs 8 weeks of expewriment for the same group, .			

1.3. Serum Insulin Resistance (IR)

Similarly, the effect of HFD on insulin resistant was obvious in HFD group after 8 weeks of diet exposure. There were significant differences ($P<0.05$) in insulin resistance at the end of experiment in all experimental groups when compare with each other table (1-4). The highest elevation was in HFD compared with CC and HFD+M groups, however, there were slight significant differences in the insulin Resistance between HFD+M (1.926± 0.10) and CC group (1.746± 0.021) at 8 weeks.

Groups Time	CC	HFD	HFDM
Zero time	0.943± 0.057 Aa	1.0075± 0.064 Aa	1.001± 0.030 Aa
8 Weeks	1.746± 0.021 Ab	7.259± 0.038 Bb	1.926± 0.10 Cb
Data represented as mean ± SEM, n = 8 each group. *Upper-case letters indicate the differences between groups in the same period of time. *Lower-case letters indicate the differences between. zero time vs 8 weeks of expewriment for the same group, .			

1.4. Effect of High Fat Diet and melatonin on serum Leptin level (ng/ ml)

Furthermore, there was a significant increase ($P<0.05$) in the serum Leptin level in the HFD groups (13.618± 0.100) at 8 weeks when compare with HFD at zero time and the other groups at the same period of timetable (1-5).

Groups Time	CC	HFD	HFDM
Zero time	5.655± 0.194 Aa	5.82± 0.186 Aa	5.788± 0.163 Aa
8 Weeks	6.921± 0.024 Ab	13.618± 0.100 Bb	6.803± 0.006 Cb
Data represented as mean ± SEM, n = 8 each group. *Upper-case letters indicate the differences between groups in the same period of time. *Lower-case letters indicate the differences between . zero time vs 8 weeks of expewriment for the same group, .			

1.5. Effect of Melatonin and HFD on Retroperitoneal fat weight / body weight ratio (%):

A statistical analysis of the obtained data revealed that Retroperitoneal fat mass / body weight was significant differed ($P<0.05$) in all experimental groups compared with each others table (1-6).

0	CC	HFD	HFDM
8 Weeks	2.147± 0.005 A	2.369± 0.005 B	1.964± 0.015 C
Data represented as mean ± SEM, n = 8 each group. *Upper-case letters indicate the differences between groups.			

1.6. Effect of Melatonin and HFD on body weight (gm)

Body weight gain significantly increased ($P<0.05$) at each time point from the first weeks onwards up to 8 in both CC and HFD group Table (1-7). Body weight in the HFD+M group remained lower than in the HFD group and CC group from week 6 until the end of the 8-week experiment, the body weight (grams) in Control group (314±5.586) was significantly higher ($p<0.05$) than weight of HFD animals (280±4.107)

and weight of animals fed HFD and injected melatonin.

Groups Time	CC	HFD	HFDM
1 wk	195± 5.580 Aa	213± 4.333 Aa	191± 7.448 Aa
2 wk	207± 5.854 Ab	227± 4.549 Ab	203± 8.079 Ab
3 wk	221± 5.924 Ac	245± 4.432 Ac	211± 7.845 Ac
4 wk	237± 6.141 Ad	262± 4.181 Ad	218± 7.860 Ad
5 wk	264± 5.878 Ae	270± 4.537 Ae	221± 8.047 Ad
6 wk	290± 5.912 Af	276± 4.181 Af	218± 8.411 Bcd
7 wk	300±5.737 Ag	279±4.094 Ag	216±7.699 Bcd
8 wk	314±5.586 Ah	280±4.107 Bg	217±8.047 Ccd

Data represented as mean ± SEM, n = 8 each group.
*Upper-case letters indicate the differences between groups in the same period of time.
*Lower-case letters indicate the differences between . zero time vs 8 weeks of expewriment for the same group, .

6. Discussion

The finding of the current study reveal that melatonin can protect from hyper glycemin the melatonin mentain the serun glucose and insulin near the normal rang when compar with control group and melatonin can reduce the higher leptin that cause by high fat diet and protect aginas the obesity and decrease the fat and mass of fat around tisse and organ

Is result agreed with (20), showed blood glucose increased after one month on HFD feeding and remained elevated throughout the sex month study period. Serum insulin were increased progressively in a time dependent manner, progressive changes in glucose uptake and GLUT-4gene expression were also observed during sex months of HFD feeding. moreover, this study was agreed with (21) who study Glucose mediates insulin sensitivity via a hepatoportal mechanism in high-fat-fed rats fed for three weeks and found the glucose and insulin resistance was significantly increased compared to control group. These changes in circulating glucose and insulin levels induced by HFD were further reflected in a significant increase in the HOMA-IR index, a quantitative measure of insulin resistance, which appeared at week 8 and augmented at week 12, although no change was seen in earlier time points(22), Consistently, in the HFD-fed mice at week 12, insulin resistance as indicated by a 5.3-fold increase in HOMA-IR index relative to control group (22).

Accumulation of excess fat in muscle and adipose tissue in insulin resistance and type 2 diabetes may be linked with defective mitochondrial oxidative phosphorylation, High-fat overfeeding increases fasting glucose levels due to increased hepatic glucose production, the increased insulin secretion may compensate for hepatic insulin resistance possibly mediated by elevated GIP secretion. Increased insulin secretion precedes the development of peripheral insulin resistance, mitochondrial dysfunction (23). Several metabolic and hormonal factors influence the synthesis and secretion of leptin in the body, such as cytokines, fatty acids, glucose, and insulin (24). Leptin is a satiety hormone and may increase peripheral insulin sensitivity as well as hepatic glucose production. Furthermore, adiponectin increases both hepatic and peripheral insulin sensitivity (25). Glucose taken from the blood is actively oxidized in the skeletal muscles and brown adipose tissue. Therefore, reduced glucose uptake in those tissues in the rats fed a high-fat diet may contribute to the higher plasma glucose level observed in those rats (26). These results suggest that high-fat diet impairs glucose metabolism in muscle by reducing transcription of GLUT4 without affecting gene expression of insulin receptor (27,28). Melatonin has been confirmed to improve induce -cell regeneration in the pancreas (29), promote hepatic glycogen synthesis thus reducing the elevation of glucose level in rodents (30). Melatonin is a powerful antioxidant and reduce blood glucose (31). Chronic high blood glucose levels might lead to mitochondrial dysfunction and trigger undesirable apoptosis in T2DM, the pineal hormone melatonin has been shown to regulate apoptosis the anti-apoptotic effects of melatonin were partly mediated by the melatonin receptor 2 (32). Leptin and TNF-α are involved in the pathogenesis of obesity and insulin resistance (33), The results of studies showed that leptin concentration correlates positively with BW and Body mass index (BMI) in type 2 diabetes condition (34), Insulin resistance is often associated with obesity and hyperleptinemia and leads to increased expression of the obesogenic gene and increased leptin level (35), study confirm that there is a high correlation between leptin, TNF-α, and insulin and these correlations cause many disorders in people with diabetes, Plasma leptin levels are directly related to body fat stores and respond to changes in the body's energy exchange (36).so our result show rat exposed to High fat diet showed an increase in amount of fat, for instance: abdominal fat and retroperitoneal fat, that means increase in leptin secreted from these fats. daily melatonin administration at middle age suppressed male rat intraabdominal visceral fat, plasma leptin, and plasma insulin to youthful levels (37). The sleep disturbance causes obesity with increased lipid accumulation in adipose tissue, Research indicates that melatonin plays a vital role in hormonal regulation and energy metabolism, including leptin signaling and secretion (38). These findings support the use of melatonin as a potential therapeutic treatment against leptin-associated disorders by

(39). Melatonin, a circadian hormone, has been reported to improve host lipid metabolism by reprogramming the gut microbiota, which also exhibits rhythmicity in a light/dark cycle, However, the effect of the administration of exogenous melatonin on the diurnal variation in the gut microbiota in mice fed a high-fat diet (HFD) (40). Research now shows that melatonin may increase metabolism and improve our ability to lose weight. Therefore, we could suggesting that melatonin fights fat in two major ways: it has the ability to assist in turning fat into energy rather than storing it and it improves thermogenic capacity of the mitochondria. melatonin greatly affected fat deposition, and hepatic Long Chain Fatty Acid supply and the expression of genes associated with lipogenesis and lipolysis (41 ,42).

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