# Effect of Melatonin ON Obesity and Lipid Profile in High Fat–Fed Rats

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**Abstract: Background**: A worldwide increase in the incidence of obesity indicates the unsucceful battle against this disorder. Obesity and the associated health problems urgently require effective strategies of treatment. Thus, melatonin, a tryptophan derivative, and naturally occurring substance with no reported toxicity may serve as a novel approach for treatment of obesity. **Objective:** The objective of this study was to investigate the effect of melatonin on obesity and lipid profile in male Wistar rats. **Material and Methods:** Forty male Wistar rats were divided into 4 groups of 10 animals for each, control group fed standard normal chow diet, obese control group fed high fat diet (HFD), normal group fed standard normal chow diet and treated with melatonin in a dose of 10mg/kg/day orally for 6 weeks and obese group fed HFD and treated with melatonin in a dose of 10mg/kg/day orally for 6 weeks with continuous HFD. At the end of experiment, body weight and food intake were determined. Then, the animals were scarificed and blood samples were collected for determination of triglycerides (TG), HDL-cholesterol, LDL-cholesterol, total cholesterol (TC), blood glucose and insulin levels. **Results:** In HFD–fed rats, melatonin significantly decreased body weight, but did not affect food intake. Melatonin significantly decreased plasma TG, LDL-cholesterol, glucose and insulin levels but it significantly increased HDL-cholesterol. While, TC levels were not changed. However, in normal chow diet–fed rats, melatonin only significantly increased HDL–cholesterol levels, but it had no effect on body weight, food intake and all other measured metabolic parameters. **Conclusion:** These data demonstrated that melatonin may act as a regulator of body weight in a model of obesity and may prevent some of the side effects on glucose homeostasis such as decreased insulin sensitivity.
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**Keywords:** Obesity, melatonin, Wister rats, high fat diet, triglycerides.

## 1. Introduction

Obesity and the associated metabolic pathologies are the most common and detrimental metabolic diseases and it has become a global epidemic disease[1]. In contrast to our ancestors, in recent decades, the food supply has become abundant and constantly available and it is also rich in energy. In addition, physical activity of modern humans has dramatically decreased[2]. Considering the rapidity of these changes, the human genome has been unable to adapt to such acute changes in the lifestyle of humans. The extra energy obtained from the diet is stored in the body as fat. As a result, obesity is an inevitable consequence[3].

Obesity is directly or indirectly associated with a variety of health disorders including cardiovascular disease, diabetes, stroke, arthritis and premature death[4]. Especially within the last decade, much effort has been spent in an attempt to decrease the incidence of obesity; these measures have included dietary management, promotion of physical activity and pharmacological interventions. However, the outcomes have been less than optimal. The incidence of obesity continues to rise not only in adults but also in children[5].

Melatonin is a neurohormone produced at night mainly by the pineal gland. It is also produced locally in many other tissues as asterocytes, lymphocytes, retina, bone marrow, ovary, testis, gut and skin[6]. Its synthesis is under the control of postganglionic sympathetic nerves. This ubiquitously acting hormone can interact both with protein receptors and lipid bilayers either at the cell membrane or at the nuclear level. Melatonin can cross–multilamellar lipid vesicles, and can easily pass through the cell membrane and bathe every part of the cell. The biological action of the hormone is likely to be at the membrane level, either via its interaction with membrane receptors, and/or as a lipoperoxidation radical scavenger[7].

Melatonin is involved in many physiological functions such as sleep promotion, circadian rhythm regulation[8], modulation of immune responsiveness, and the control of seasonally reproductive animals[9] and it is involved in numerous other functions, including regulation of body weight and energy balance[10]. Locally produced melatonin and several of its metabolites, which also effective scavengers, act as effective antioxidant and anti-inflammatory agents[11-12].

Melatonin also present in foodstuffs including vegetables, fruits, herbs, olive oil [13-15]. It has been classified as a food supplement in the USA, and its

consumption has not been associated with any serious adverse effects or toxicities[9].

Thus, it is worth to investigate the effect of melatonin supplement on the body weight, food intake and lipid profile in obese high–fat fed rats.

## 2.Materials and methods

**Animals:**

Forty male Wistar rats were about (5-7 weeks old), their weight range between 180-200gm. They were housed in standard cages and maintained at standard conditions with controlled light cycle (the light cycle was 12-h light and 12-h darkness). Rats were kept at a room temperature (22±2°C). Food and water were available.

Rats were fed on standard rodent chow diet (composed of 64.2% carbohydrate, 30.7% protein and 5.1% fat)[16]. But, the rats in obese groups received special food regimen for induction of obesity.

**Induction of obesity:**

Induction of obesity was carried out using high fat diet (HFD) composed of (70% fat, 20% carbohydrates and 10% protein)[17]. The animals were weighed three times a week until the average body weight reached a significant difference of at least 20gm between the rats fed–HFD and those fed–standard chow diet. Then, the animals in the obese groups were kept on HFD until the end of experiment.

**Chemicals:**

Melatonin was obtained from (Sigma chemical Co). It was dissolved in a minimum volume of absolute ethanol and diluted in the drinking water to yield a dose of 10mg/kg/day[18] and administrated daily orally for 6weeks. Fresh melatonin solution was prepared twice a week, and the melatonin dose was adjusted to the body weight throughout the study period. Water bottles were covered with aluminum foil to be protected from light.

**Experimental design:**

The animals were divided into four groups (each n=10): group I (normal control group fed–standard chow diet), group II (obese control group fed–HFD), group III (normal group fed–standard chow diet and treated with melatonin in a dose of 10mg/kg/day orally for 6 weeks), group IV (obese group fed–HFD, then treated with melatonin in a dose of 10mg/kg/day orally for 6 weeks with continuous HFD).

**Body weight assay:**

All rats were weighed at the beginning of the experiment and weekly at fixed times throughout the entire course of the experiment.

Final body weight was measured after 6 weeks of the treatment.

**Assay of food intake:**

Food was placed in small jars inserted into larger jars to collect any spilled food. The spilled food was calculated and added to subsequent feeds. The feeder jars were refilled daily. Both average daily and weekly food intake were calculated.

Total food intake was determined through the six weeks period of the experiment.

**Biochemical assays:**

At the end of the treatment period, the animals were sacrificed, then blood was collected into tubes containing EDTA and were centrifuged at 3000 r.p.m for 20 minutes to separate plasma for determination of: triglycerides (TG) level according to the method described by Bucolo *et al.,*[19], high density lipoprotein (HDL)-cholesterol level was measured by Finley[20]. low density lipoprotein (LDL)-cholesterol was measured according to the method described by Friedewald *et al.,*[21], total cholesterol (TC) level was measured by Flegg[22], glucose level was measured according to the method described by Trinder[23] and insulin level was measured by Chevenne *et al.,*[24].

**Statistical analysis:**

The data were expressed as the mean ± standard deviation. Data from studies were analyzed using one–way ANOVA.

*P*-values <0.05 were considered statistically significant. All the analyses were performed using SPSS for windows (Version 10.0).

## 3.Results

A summary of our results were shown in table (1) and figure (1) as following:

**Changes in body weight:**

The intake of HFD was associated with a significant increase of body weight in the rats of obese group (280.6±7.32g) as compared to those in normal control group (195±6.94g).

The treatment of melatonin for 6weeks was associated with significant reduction of body weight in obese rats (259.6±18.12g) as compared with control obese received no melatonin treatment, but the body weight still significantly higher as compared to normal control.

Melatonin treatment did not significantly affect body weight in the normal rats (193.8±8.72g) as compared to normal control

**Changes in total food intake:**

Compared with the normal control group (676.5±17.08g/6weeks), total food intake was significantly higher in the obese control group (1533.4±17.99 g/6weeks).

Melatonin treatment was associated with insignificant change of food intake in both obese rats (1529.3±15.36g/6weeks) and in normal rats

(673.5±16.64g/6weeks) when compared with the obese control and normal control groups respectively.

**Changes in lipid parameters:**

TG levels were higher in obese control rats (210.9±10.35mg/dl) compared to normal control rats (72.4±6.96mg/dl).

Melatonin treatment of obese rats significantly reduced the hypertriglyceridemia (178.7±16.31mg/dl) as compared to obese control. But, melatonin treatment insignificantly affected TG levels in normal rats (71.4±6.80mg/dl).

As regard HDL-cholesterol levels, they were significantly higher in obese rats (80.3±4.35mg/dl) as compared to normal control (65.4±5.05mg/dl), and melatonin treatment significantly increased HDL-cholesterol levels in both obese rats (96.7±5.87mg/dl) and normal rats (73.2±3.56mg/dl) as compared to obese control and normal control groups respectively.

While, LDL-cholesterol levels did not significantly differ between normal control (5.44±0.56mg/dl) and obese control rats (5.38±0.79mg/dl). But, they were significantly decreased by melatonin treatment in HFD-fed obese rats (4.26±0.32mg/dl) as compared to obese control. However, melatonin treatment did not significantly affect LDL–cholesterol levels in normal rats (5.24±0.61mg/dl).

TC levels were significantly higher in obese control rats (100.6±2.96mg/dl) as compared to normal control rats (81.3±2.58mg/dl).

Melatonin treatment did not affect TC levels in either obese rats (100.3±2.92mg/dl) or normal rats (80.4±2.99mg/dl) as compared to obese control and normal control respectively.

**Changes in plasma glucose and insulin:**

Compared with the normal control group (88.7±4.87mg/dl), the plasma glucose levels were insignificantly higher in obese control group (89.9±4.04mg/dl).

Melatonin treatment significantly decreased glucose levels in obese rats (77.2±5.10mg/dl) as compared to obese control but, did not affect glucose levels in normal rats (84.9±4.24mg/dl) as compared to normal control rats.

While, plasma insulin levels were significantly increased in obese control group (18.0±1.67µIU/ml) as compared to normal control (10.5±1.04µIU/ml).

Melatonin treatment significantly lowered the insulinaemia in obese rats (16.2±1.39µIU/ml). But, it did not affect insulin levels in normal rats.

**Table (1): Effect of melatonin on final body weight, total food intake, lipid parameters, plasma glucose and insulin levels in normal and obese rats:**

| Parameters | Normal control (n=10) | Obese control (n=10) | Normal treated with melatonin (n=10) | Obese treated with melatonin (n=10) |
|---|---|---|---|---|
| **Final body weight (g)** | 195±6.94 | 280.6±7.32[a] | 193.8±8.72[b] | 259.6±18.12[a,b,c] |
| **Total food intake (g/6 weeks)** | 676.5±17.08 | 1533.4±17.99[a] | 673.5±16.64[b] | 1529.3±15.36[a,c] |
| **TG (mg/dl)** | 72.4±6.96 | 210.9±10.35[a] | 71.4±6.80[b] | 178.7±16.31[a,b,c] |
| **HDL–cholesterol (mg/dl)** | 65.4±5.05 | 80.3±4.35[a] | 73.2±3.56[a,b] | 96.7±5.87[a,b,c] |
| **LDL–cholesterol(mg/dl)** | 5.44±0.56 | 5.38±0.79 | 5.24±0.61 | 4.26±0.32[a,b,c] |
| **TC (mg/dl)** | 81.3±2.58 | 100.6±2.96[a] | 80.4±2.99[b] | 100.3±2.92[a,c] |
| **Glucose (mg/dl)** | 88.7±4.87 | 89.9±4.04 | 84.9±4.24 | 77.2±5.10[a,b,c] |
| **Insulin (µIU/ml)** | 10.5±1.04 | 18.0±1.67[a] | 10.3±0.98[b] | 16.2±1.39[a,,b,c] |

**Data are given as mean ± SD.**

**[a]*P*< 0.05 compared to control. [b]*P*< 0.05 compared to obese control. [c]*P*< 0.05 compared to normal group treated with melatonin.**

## 4.Discussion

Melatonin is the chief hormone of the pineal gland that interacts with a variety of different cells[7]. In humans, melatonin receptors has been detected in the retina, brain, suprachiasmatic nucleus, central and peripheral arteries, kidneys, pancreas, adipocytes and immune cells[25,26].

It is known that melatonin exerts antioxidant, anti-inflammatory, anti-hyperlipidemic and anti-hypertensive actions and also modulates insulin secretion and action[27-29]. There are reports showing that melatonin–insulin interactions and relationship between melatonin–insulin ratio and lipid profile may exist in patients with metabolic syndrome[30] and that melatonin therapy improves blood pressure, lipid profile and parameters of oxidative stress in patients with metabolic syndrome[31].

The present study has demonstrated that melatonin treatment of obese rats was associated with a reduction in body weight without affecting food intake.

These effects of melatonin are supported by several observations[18,.32]. The weight–loss–promoting effect of melatonin may be attributable to

an increase in energy expenditure especially by brown adipose tissue (BAT)[9]. In this line, various rodent studies have demonstrated that melatonin increases BAT mass and BAT activity. Although, the exact mechanisms whereby melatonin influences BAT physiology are unknown, there is indirect evidence suggesting several potential explanations[9].

Thus, through its M1/M2 membrane receptors, melatonin can affect BAT mass either by activation of the sympathetic nervous system and its consequences in term of lipolysis and adipose tissue plasticity[33,34], or by direct activation of the protein kinase C (PKC) pathway in BAT cells, which in turn leads to up-regulation of growth factors for brown adipocyte differentiation and mitochondrial biogenesis[35].

Melatonin can also act via nuclear receptors in brown adipose cells to achieve the same effect. Furthermore, melatonin can promote BAT thermogenesis through activation of the mitochondrial uncoupling protein1 (UCP1), either directly or by activating type 2 thyroxin 5'-deiodinase to increase intracellular tri-iodothyronine ($T_3$) levels[36]. Finally, it has been speculated that melatonin and its metabolites can protect the mitochondria from oxidative stress[12,37].

Melatonin appears to act only when energy balance is disturbed, because such effects were not obtained when treatment was performed in normal rats[38,39], and this was in agree with our results that showed that melatonin treatment did not affect either body weight or food intake in normal rats.

In our present study, melatonin administration significantly improved the lipid profile of the obese rats by decreasing TG and LDL–cholesterol levels and increasing HDL cholesterol levels without affecting the total cholesterol levels.

Similar findings were reported by Prunet-Marcassus *et al.,*[16]. The effect of melatonin in lowering the hypertriglyceredemia can be explained by its suppression of visceral fat without affecting subcutaneous deposits[40.41], and leading to enhanced lipoprotein lipase activity and reduced lipolytic activity in visceral adipose tissue[40].

In our study, melatonin significantly increased plasma HDL-cholesterol without affecting TC levels in both obese and normal rats. The precise mechanism by which melatonin increases HDL-cholesterol has yet to be elucidated but, may involve augmented cholesterol estrifiaction[42] mediated by higher lecithin–cholesterol acyltransferase activity[43].

Our present study showed that melatonin treatment significantly reduced plasma LDL-cholesterol levels in obese rats.

The LDL–cholesterol lowering effect of melatonin may contribute to its role in atherogenesis prevention[44,45]. Other authors also found that melatonin significantly reduced LDL-cholesterol plasma levels, but in rats fed on a high cholesterol diet[46,47]. The mechanism of this effect of melatonin may be via inhibition of cholesterol absorption[46]. Other mechanisms may include an increase of LDL-receptors synthesis/activity, inhibition of cholesterol synthesis, or enhancement of cholesterol catabolism to bile acids[48,49].

Our study showed that, plasma glucose levels were insignificantly increased in obese rats. However, melatonin administration significantly decreased this glycaemia in obese rats.

The ability of melatonin to affect plasma glucose levels is due to its ability to increase insulin output by pancreatic B–cells. Moreover, melatonin may act directly on the liver to elevate the plasma glucose level, and changes in plasma glucose level itself may in turn affect hepatic melatonin binding[50].

Our study revealed that plasma insulin levels significantly increased in obese rats. While, melatonin treatment significantly lowered this insulinaemia.

The reduction in insulin secretion in obese rats may be due to improvement in insulin sensitivity by melatonin treatment[51]. But in other studies, melatonin has no effect on plasma insulin but only it decreased the elevated plasma glucose in obese rats[52].

In a study performed in a diet–induced murine model of obesity, melatonin significantly improved insulin sensitivity and glucose tolerance[53].

**Conclusion:**

From our results, we demonstrated that melatonin reduced body weight, plasma TG, LDL–cholesterol, glucose and insulin levels, and increased HDL–cholesterol levels without affecting either TC level or food intake in obese rats.

These overall findings suggest that melatonin should be exploited as a therapeutic tool to prevent or reverse the harmful effects of obesity and its related metabolic disorders as dyslipidemia and insulin resistance.

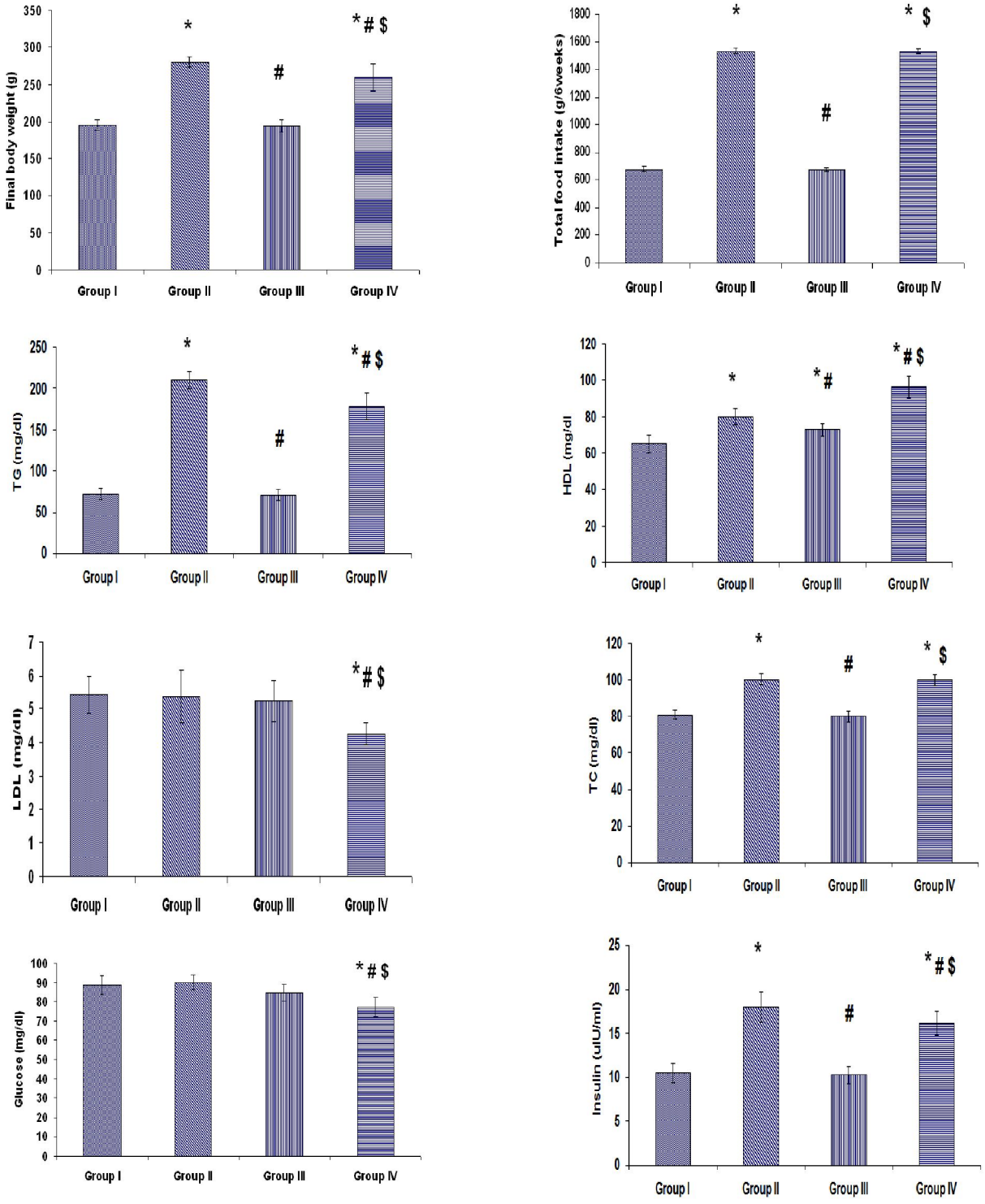


**Figure (1): Effect of melatonin on final body weight, total food intake, lipid parameters, plasma glucose and insulin levels in normal and obese rats.**
*** *P*< 0.05 compared to normal control. # *P*< 0.05 compared to control obese. $ *P*< 0.05 compared normal group treated with melatonin.**

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