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Studies on the effects of dietary supplementation of melatonin on serum metabolic profile in broiler chickens

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Abstract
The present study was undertaken to evaluate the effect of the dietary melatonin supplementation on serum metabolic profile in broiler chickens. Day old commercial broiler chicks (240 Nos) weighing around 45-55g were procured and reared in common for 14 days. After 14 days of rearing, the broilers were divided randomly into four groups in triplicates with 20 birds in each group in three replicates. They were allotted to different dietary supplements; Group I comprised of control group fed basal diet; for Group II, the basal Diet was supplemented with Melatonin @ 20 mg/kg feed; for Group III, with Melatonin @ 30 mg/kg feed and for Group IV, with Melatonin @ 40 mg/kg feed. Blood samples were collected at 14th, 28th and 42nd day during morning hours and the serum samples were analysed for biochemical parameters. In the present study, the serum glucose levels and blood urea nitrogen values levels did not vary significantly among the groups. A significantly higher serum total protein levels were noted in Group III and IV at day 42 compared to the control group. The levels of serum cholesterol, triglycerides levels were significantly (p<0.05) lower at day 42 in Group III and IV compared to Group I control. It is concluded that the supplementation of melatonin in the diet of broilers have positive influence on biochemical parameters.

Keywords: Melatonin, broiler chicken, serum biochemistry

Introduction

The poultry industry is concentrating on increasing operational efficiencies by boosting feed conversion ratios (FCR), which indicate higher bird weight as a percentage of feed utilized, in the light of high cost of feed. Melatonin's many biological roles, which go beyond its well-known regulatory role in circadian rhythms, have made supplementing with this hormone more significant in recent years. Nearly all living things, including microbes, plants, and animals, contain melatonin (N-acetyl-5-methoxytryptamine) (Mannino *et al.*, 2021) [16].

According to Egbuniwe and Ayo (2016) [11], broiler chickens that secrete insufficient amounts of melatonin are linked to metabolic and physiological disorders that result in breeding diseases and deaths, as well as financial losses and a number of detrimental aspects of animal welfare, such as fearful reactions in the birds. Calislar *et al.* (2018) [8] reported similar findings. The most significant function of melatonin in the body is its involvement in the antioxidant system and defense of cells against the damaging effects of free radicals (Zhao *et al.*, 2019) [38]. Melatonin also positively influences growth performance, feed intake and feed conversion efficiency, the morphology of intestinal mucosa and circulating growth hormone levels (Zeman *et al.*, 1999; Brennan *et al.*, 2002; Abbas *et al.*, 2007; Sinkalu, 2012 and Akbarian *et al.*, 2014) [36, 6, 1, 32, 3].

Different lighting regimes used in intensive broiler chicken production have an impact on the natural cycle of melatonin secretion, a hormone involved in several bodily physiological functions. Melatonin has been linked in a number of studies to changes in chicken growth and metabolism. Melatonin promotes feed conversion, according to several research (Osei *et al.*, 1989) [21], however the exact mechanisms of action are unknown. Melatonin may influence the effectiveness of nutrition utilization at multiple levels.

This hormone can modulate intermediary metabolism (Zeman *et al.*, 1993) [37], interact with transcriptional factors (Chuang *et al.*, 1996) [9], impact thermoregulatory mechanisms (Rozenboim *et al.*, 1998) [28], influence energy metabolism (Apeldoorn *et al.*, 1999) [5], and affect growth hormone production (Zeman *et al.*, 1999) [36].

Perusal of literature revealed a sizeable study on dietary melatonin supplementation on metabolic profile and with a meagre literature available on the effects of dietary melatonin supplementation on hormonal, immune and metabolic effects in broiler chicken. Hence, in this scenario, this study on the effects of dietary supplementation of melatonin on biochemical parameters in broiler chickens was undertaken

Materials and Methods

The present study was conducted to study the effect of the supplementation of melatonin on serum metabolic profile in broiler chickens. The experiment was carried out in the Department of Veterinary Physiology and Department of Veterinary Pathology, Veterinary College, KVAFSU, Hebbal, Bengaluru, during September and October, 2023 for a period of 42 days (6 weeks).

Melatonin

Melatonin extra pure, 99% (25 grams) crystalline powder was obtained from Sisco Research Laboratory (SRL) and stored at-20 °C until use.

Experiment Design

The experiment was carried out in two hundred and forty Cobb broiler chickens and all the broilers were provided with similar management inputs during study period. Day old commercial broiler chicks (240 Nos) weighing around 45 to 55g were procured from Pragathi Hatcheries, Doddaballapur Taluk, Bengaluru and reared in common for 14 days for acclimatization period on broiler diet (as per BIS, 2007). After 14 days of rearing, the broilers were divided randomly into four groups in triplicates with 20 birds in each group in three replicates. They were allotted to different dietary supplements as mentioned below. Institutional Animal Ethics Committee (IAEC) permission was obtained to carry out the study (No. VCH/IAEC/2023/21) dated 17.08.2023.

Groups	Description
Group I	Control group (Basal Diet)
Group II	Basal Diet supplemented with Melatonin @ 20 mg/kg feed
Group III	Basal Diet supplemented with Melatonin @ 30 mg/kg feed
Group IV	Basal Diet supplemented with Melatonin @ 40 mg/kg feed

Vaccination

The day-old broiler chicks were immunized against Marek's disease in hatchery, on 7th day chicks were vaccinated against Ranikhet disease (Newcastle disease) with B1 strain through intra ocular route and on 21st day booster dose of NDV with Lasota strain through drinking water, and Gumboro disease (Infectious Bursal Disease: IBD) with intermediate strain on 14th day through intraocular and IBD booster on 28th day through drinking water.

Feeding and Watering

The ingredients of different types of feeds such as pre-starter, starter and finisher and their nutrient composition is provided in Appendix 1. All the broiler chicks were provided *ad-libitum* feed and fresh water (NRC, 1994) [19].

Climate and Weather

All the broiler chicks during acclimatization period for first 14 days were kept for brooding by providing light source of 4×100watt incandescent bulb for 24 hrs. Climatic parameters such as temperature and relative humidity were recorded twice a day (morning at 11.30 AM and afternoon at 2.30 PM) by using dry and wet bulb thermometer.

Mortality of birds

In the present study, it was observed that three birds died in Group I, two bird form Group II, two bird died in Group III and three bird from Group IV. They were replaced by other birds which were maintained as additional birds in each group. Dead birds were disposed by following biomedical waste disposal procedure of the college as per the guidelines of Institutional Biosafety Committee.

Collection of Blood sample

Blood sample of 3mL was from each bird were collected in clot activated vacutainer at fortnightly intervals *i.e.*, at 14th, 28th and 42nd day during morning hours and blood samples were allowed to clot for 30 min and they were centrifuged at 3000 rpm for 20 min and serum samples were separated in Eppendorf tubes and stored at-20 °C for estimation of serum biochemical, antioxidant, hormonal and immune parameters.

Estimation of Biochemical Parameters

The serum samples were analysed for biochemical parameters such as glucose, total protein, albumin, cholesterol, triglycerides, blood urea nitrogen using micro lab 300 semi-automated biochemical analyzer (supplied by Merck Pvt. Ltd, Mumbai) using SWEMED® diagnostic kits, following the instruction and procedure supplied with the diagnostic kits.

Statistical Analysis

The data obtained were analysed statistically by two-way ANOVA with the application of Bonferroni post-test using 'GraphPad Prism' version 9.0.0 (121) computerized software, San Diego, CA, USA. The values were expressed as Mean ± Standard Error and the level of significance or non-significance was determined at P value of 0.05, as per the methods described by Snedecor and Cochran (1994) [33].

Results and Discussion

Serum glucose (mg/dL)

Broiler chickens' serum glucose levels are a crucial window into their general health and metabolic status. Serum glucose levels in clinically healthy broiler chicken normally vary from 137 mg/dL to 363 mg/dL, depending on the measuring technique (Goodwin *et al.*, 1994) [13].

The serum glucose level did not vary significantly among the groups although the melatonin supplementation Group IV had a numerically highest serum glucose level at day 42. The serum glucose levels did not vary significantly along the study period in both control and the melatonin supplemented groups, although results indicated a dose dependent increase in the serum glucose level at day 42 in all the melatonin supplemented groups with highest in Group IV at day 42 when compared to other melatonin supplemented groups such as Group II and III and the lowest glucose concentration was noted in control group at day 42. (Table-1)

The presence of high affinity melatonin receptors present in hepatocytes (Poon *et al.*, 2001) [25] as well as increased glucose tolerance and decreased serum insulin level upon melatonin supplementation was attributed to the mechanism by which melatonin could raise serum glucose levels (Anisimov *et al.*, 1994) [4]. Islets of Langerhans express melatonin receptors MT1 and MT2, which can regulate β-cell-dependent insulin secretion and α-cell-dependent glucagon secretion (Peschke *et al.*, 2013) [23]. Changes in melatonin levels are crucial for the islets' ability to regulate blood glucose (Navarro-Alarcon *et al.*, 2014 and Peschke *et al.*, 2013) [23]. Studies on diabetic rat models revealed an inverse link between insulin and melatonin secretion (Peschke *et al.*, 2013) [23]. Moreover, insulin production in response to glucose was inhibited by melatonin (Navarro-Alarcon *et al.*, 2014 and Peschke *et al.*, 2008) [20, 24]. This suggests the melatonin supplementation in animal could increase hepatic gluconeogenesis, most likely through activation of MT2 receptors. Further, the signalling patterns of uncommon MT2 receptor polymorphisms that have been linked to an increased risk of type-II diabetes mellitus are providing additional intriguing new information (Karamitri *et al.*, 2018) [15].

Research on human islets indicate that the melatonin raises intracellular calcium levels and triggers the production of glucagon and insulin from α-cells and β-cells, respectively (Ramracheya *et al.*, 2008) [27]. This is most likely due to paracrine input from α-cells to β-cells that secrete insulin.

Crucially, using melatonin or the melatonin receptor agonist such as ramelteon to activate melatonin signalling in human islets over an extended period of time (of a duration that resembles night exposure) raises islet sensitivity to cAMP, which in turn increases insulin secretion, just like in rodent cells (Costes *et al.*, 2015) [10]. Melatonin signalling improves insulin secretion and β-cell survival, as demonstrated by the preservation of histone acetyl transferase p300 protein levels (Ruiz *et al.*, 2018) [29] and the reduction of proteotoxicity-induced cell apoptosis and oxidative stress in human islets exposed to chronic hyperglycaemia and in islets from patients with type 2 diabetes (Costes *et al.*, 2015) [10].

In the present study the increase in glucose could be attributed to the presence of high-affinity melatonin receptors in hepatocytes, leading to enhanced hepatic gluconeogenesis, as well as modulation of insulin and glucagon secretion through melatonin receptor pathways.

Serum total protein and albumin (g/dL)

A crucial indicator for assessing the nutritional and physiological status of broiler chickens is their serum total protein levels. These preserve colloid osmotic pressure, function as enzymes or catalysts in biochemical reactions, are crucial for haemostasis, preserve the acid-base balance, control hormone levels and act as antibodies, which are the body's defence systems. Additionally, they carry and transport the majority of plasma constituents (Murray *et al.*, 2000; Voet *et al.*, 1999 and Kaneko *et al.*, 2008) [18, 35, 14].

The serum total protein levels did not vary significantly among the groups at day 14 and day 28. At day 42 significantly higher serum total protein levels were noted in Groups III and IV compared to the control group. The melatonin supplementation Group IV had highest serum total protein concentration at day 42 in this study. The serum total protein did not vary significantly along the study period in both control and the melatonin supplemented groups, although results indicated a dose dependent increase in the serum total protein concentration at day 42 in all the melatonin supplemented groups with highest in Group IV when compared to other melatonin supplemented groups II and III and the lowest serum total protein concentration was noted in control group at day 42. (Table-1)

Non significant (p>0.05) variation was observed among the groups and between the groups. However, the serum albumin concentration was numerically higher in all the melatonin supplemented groups at day 42 compared to control group, with highest serum albumin concentration in Group IV and lowest in control group.

These findings were in accordance with the reports of Patil *et al.* (2013) [22] wherein they reported that the supplementation of melatonin numerically increased the serum protein levels when compared to toxin fed birds.

In the present study the increase in serum total protein in Group III and IV and serum albumin in Group IV could be attributed to the protection of liver by the melatonin that acts as an antioxidant.

Serum cholesterol and triglycerides (mg/dL)

The serum cholesterol levels were significantly (p<0.05) lower at day 42 in Groups III and IV compared to Group I and II and no significant (p>0.05) differences were noted among Groups II and III. Similarly, no significant differences were noted in Group II and control group. At day 14 and day 28 no significant differences were noted in serum cholesterol levels among melatonin supplemented groups and control group. Along the study period age dependent increase in serum cholesterol levels were noted with significantly highest values at day 42 in all the groups. In melatonin supplemented group such as Group II, III and IV significantly higher serum cholesterol values were observed at day 28 and day 42 compared to day 14. In control group the serum cholesterol values were higher as age advanced between day14, day 28 and day 42. (Table-1)

On day 42, the serum triglycerides levels were significantly (p<0.05) lower in Group IV when compared to the Group I and Group II and the differences were found to be non-significant (p>0.05) among Group II and III and among Group III and IV. Age dependent significant decrease in serum triglycerides levels was observed in all the melatonin supplemented groups compared to control group.

The results of the present study were in agreement with the findings of Soltan and Hussein (2017) [34] in chickens; Sahin *et al.* (2004) [30] in Japanese quails; Esquifinoa *et al.* (1997) [12] in rats and Sandyk and Awerbuck (1994) [31] in humans. They reported that melatonin supplementation had lowering effect on serum cholesterol and triglycerides levels in these species. After reviewing the effects of melatonin supplementation on blood lipid concentrations, Mohammadi-Sartang *et al.* (2018) [17] came to the conclusion that melatonin supplementation significantly affects triglycerides and total cholesterol levels, with the effects being more pronounced at higher doses, for longer periods of time, and at higher cholesterol concentrations.

Table 1: Mean ± SE values of serum biochemicals in different groups of broiler chickens supplemented with melatonin.

Parameter	Study Groups	Day 14	Day 28	Day 42
Serum Glucose (mg/dL)	Group I	246.75 ± 9.51	231.59 ± 7.70	240.53 ± 13.31
	Group II	244.21 ± 14.03	239.57 ± 11.72	252.00 ± 4.66
	Group III	247.14 ± 6.13	247.20 ± 7.14	268.33 ± 10.71
	Group IV	251.51 ± 10.16	263.93 ± 11.65	274.08 ± 13.65
Serum Total Protein (g/dL)	Group I	4.48 ± 0.10^{a}	4.52 ± 0.13^{a}	4.18 ± 0.14^{a}
	Group II	4.36 ± 0.26^{a}	4.55 ± 0.17^{a}	4.70 ± 0.22^{ab}
	Group III	4.24 ± 0.24^{a}	4.70 ± 0.14^{a}	4.83 ± 0.16^{b}
	Group IV	4.43 ± 0.15^{a}	5.01 ± 0.16^{a}	4.90 ± 0.17^{b}
Serum Albumin (g/dL)	Group I	1.73 ± 0.12	1.79 ± 0.14	1.94 ± 0.08
	Group II	1.70 ± 0.29	1.82 ± 0.12	1.95 ± 0.18
	Group III	1.66 ± 0.17	1.80 ± 0.08	2.09 ± 0.10
	Group IV	1.81 ± 0.07	2.11 ± 0.14	2.32 ± 0.14
Serum Cholesterol (mg/dL)	Group I	$84.79 \pm 2.51^{a, x}$	$120.57 \pm 4.61^{a, y}$	$139.91 \pm 2.91^{c, z}$
	Group II	$84.55 \pm 3.25^{a, x}$	$118.17 \pm 5.33^{a, y}$	$129.12 \pm 5.68^{bc, y}$
	Group III	$81.48 \pm 2.75^{a, x}$	$113.85 \pm 4.17^{a, y}$	$117.52 \pm 2.68^{ab, y}$
	Group IV	$82.04 \pm 2.52^{a, x}$	$108.85 \pm 3.37^{a, y}$	$113.44 \pm 3.36^{a, y}$
Serum Triglycerides (mg/dL)	Group I	$43.49 \pm 3.79^{a, x}$	$52.89 \pm 4.34^{a, x}$	$62.70 \pm 4.49^{b, y}$
	Group II	$44.92 \pm 2.79^{a, x}$	$49.39 \pm 5.25^{a, x}$	$55.29 \pm 4.31^{b, x}$
	Group III	$42.04 \pm 3.19^{a, x}$	$43.55 \pm 3.61^{a, x}$	$51.76 \pm 4.80^{ab, x}$
	Group IV	$45.29 \pm 4.18^{a, x}$	$39.72 \pm 5.67^{a, x}$	$44.22 \pm 5.72^{a, x}$
Blood Urea Nitrogen (mg/dL)	Group I	1.91 ± 0.06^{x}	1.82 ± 0.07^{x}	1.71 ± 0.11^{x}
	Group II	1.87 ± 0.09^{x}	1.64 ± 0.13^{x}	1.61 ± 0.13^{x}
	Group III	1.88 ± 0.09^{x}	1.53 ± 0.09^{y}	1.44 ± 0.10^{y}
	Group IV	1.89 ± 0.08^{x}	1.44 ± 0.09^{y}	1.30 ± 0.08^{y}

Note: The values bearing different superscripts between groups (a, b, c) and between periods (x, y) for a particular parameter differ significantly ($p \leq 0.05$).

Blood urea nitrogen (mg/dL)

The blood urea nitrogen values did not differ significantly among groups and between the control and melatonin supplemented groups on day 14, 28 and 42. In Group III and IV, the blood urea nitrogen values were significantly ($p<0.05$) lower on day 28 and day 42 when compared to Day 14. However, similar differences were not noted in Group II and control group but were found to be statistically non-significant (P>0.05). (Table-1)

There are no reports in broiler chickens to compare the results of the present study. The findings were in agreement with lowered BUN levels by antioxidative effects of melatonin (Aizawa *et al.*, 1986) [12] and reversal of BUN levels by melatonin administration (Ramadan *et al.*, 2021) [26].

There are no reports in broiler chickens to compare the results of the present study. The findings were in agreement with lowered BUN levels by antioxidative effects of melatonin (Aizawa *et al.*, 1986) [2] and reversal of BUN levels by melatonin administration (Ramadan *et al.*, 2021) [26].

Conclusions

The serum glucose levels indicated a dose dependent increase in the serum glucose concentration in all the melatonin supplemented groups. The possible mechanism for the increasing the levels of serum glucose by melatonin might be due to increased glucose tolerance and decreased serum insulin upon melatonin supplementation. A dose dependent increase in the serum total protein concentration in all the melatonin supplemented groups. This may be due to ability of melatonin was able to protect liver tissues from toxic effects and stimulate liver with resultant improved protein synthesis. It is concluded that melatonin administration may have cholesterol-reducing effect and melatonin could be used therapeutically in the treatment of hypercholesterolemia.

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