

Protective effect of resveratrol co-administered with high fat diet on blood glucose homeostasis and thyroid function in rabbits

Jimoh A.^{1,*}, Tanko Y.¹, Ahmed A.², Mohammed A.¹, Ayo J. O.³

¹Department of Human Physiology, Ahmadu Bello University, Zaria, Nigeria

²Department of Pharmacognosy, Ahmadu Bello University, Zaria, Nigeria

³Department of Veterinary Physiology and Pharmacology, Ahmadu Bello University, Zaria, Nigeria

Email address:

jabdulazeez0429@gmail.com (Jimoh A.)

To cite this article:

Jimoh A., Tanko Y., Ahmed A., Mohammed A., Ayo J. O.. Protective Effect of Resveratrol Co-Administered with High Fat Diet on Blood Glucose Homeostasis and Thyroid Function in Rabbits. *Cell Biology*. Vol. 3, No. 1, 2015, pp. 19-24.

doi: 10.11648/j.cb.20150301.13

Abstract: Consumption of high fat diet rich in calorie has been associated with an increased incidence of diabetes mellitus. Deep underlying relation between diabetes mellitus and thyroid dysfunction has already been established. The aim of these experiments was to investigate the protective effect of resveratrol co-administration with high fat diet on blood glucose level and serum triiodothyronine (T₃) and thyroxine (T₄) levels in rabbits. Thirty rabbits divided into six groups of five animals (n = 5) each were used for the experiment: Group 1 = normal control (C), group 2 = high fat diet (HFD) only, group 3 = resveratrol 200 mg/kg (R200), group 4 = resveratrol 400 mg/kg (R400), group 5 = HFD + R200 and group 6 = HFD + R400. Our findings demonstrate significant (P < 0.05) decrease in blood glucose level in HFD group treated with resveratrol compared with HFD group only after 5 weeks of the experimental protocol. Significant (P < 0.05) decrease in T₃ and T₄ levels were also observed in HFD group compared to the control group. Slight increase in T₃ level was observed in HFD group treated with resveratrol but not significant (P > 0.05) compared to HFD group only. T₄ level in the HFD group showed significant (P < 0.05) decrease compared to HFD group treated with resveratrol. In conclusion, the result demonstrated that co-administration of resveratrol with HFD decreases blood glucose level and improves T₃ and T₄ levels in HFD fed rabbits.

Keywords: High Fat Diet, Blood Glucose Level, Rabbit, Thyroid Hormone

1. Introduction

The role of hyperthyroidism in diabetes was investigated in 1927 by Coller and Huggins; proving the association of hyperthyroidism, and worsening of diabetes. It was shown that surgical removal of parts of thyroid gland had an ameliorative effect on the restoration of glucose tolerance in hyperthyroid patients, suffering from co-existing diabetes [1]. There is a deep underlying relation between diabetes mellitus and thyroid dysfunction [2]. Thyroid hormones directly control insulin secretion. Hypothyroidism results into a reduction in glucose-induced insulin secretion by beta cells, and the response of beta cells to glucose or catecholamine is increased in hyperthyroidism due to increased beta cell mass. Moreover, insulin clearance is increased in thyrotoxicosis [3,4]. Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism. Excess or deficit

of the hormones can result in functional derangement of the other [5]. In hypothyroidism, glucose-induced insulin secretion by the β -cell is reduced while in hyperthyroidism, β -cell response to glucose or catecholamine stimulation appears to be increased and is accompanied by an increased β -cell mass [3,4]. The rates of glucose oxidation and glycogen synthesis are decreased in hypothyroidism due to down-regulation of glucose transporter GLUT5 in humans and impaired GLUT4 transporter in animal model [6]. Hyperthyroidism is associated with increased GLUT2 expression, as compared to the hypothyroid state [3]. Alterations in lipid metabolism further link thyroid hormone to insulin resistance [4]. Thyroid hormones-dependent fatty acid uptake is tissue specific and may be increased in both thyrotoxicosis and hypothyroidism [7]. Thyroid hormone stimulates catecholamine action, which in

turn increase lipolysis in adipose tissue, hence increasing circulating FAs [3]. The excessive consumption of high fat diet has been associated with an increased incidence of diabetes mellitus. They are enhanced by formation of oxidative stress form as a result of accumulation and adipose tissue expansion and consequently resulted into high levels of glucose which are potent inducers of cellular reactive oxygen species (ROS) [8,9,10]. Diabetes mellitus is considered as a common, growing, serious and costly, but potentially preventable public health problem [11]. Continuous consumption of calories-rich meals, junk food and sedentary lifestyle has culminated into an epidemic of diabetes worldwide. In general, High Fat Diet (HFD) is a nutritional condition that accounts for the largest incidence of metabolic syndrome in the world [12]. Defective insulin secretion leads to various metabolic aberrations in T2DM. The impairments include hyperglycaemia due to insulin-stimulated glucose uptake, up-regulated hepatic glucose production and dyslipidaemia [13]. Resveratrol (3, 5, 4'-trihydroxystilbene) is a polyphenol that occurs naturally in foods and drinks made from grapes and peanuts, and also in a number of herbal remedies, both alone and as part of plant extracts. Since then, studies have shown that resveratrol is a member of a class of compound called phytoalexins, which plants use as a defense mechanism against pathogens, and it has also shown that it prevents or slows the progression of a wide variety of illnesses, including treatment of diabetes complications [14], cancer, cardiovascular disease [15], ischemic injuries and myocardial infarction [16,17]. Information on the protective effect of resveratrol on diabetes mellitus, and thyroid function in rabbits are scanty. The present study was undertaken to assess changes in blood glucose level, Triiodothyronine and thyroxine level in high fat diet fed rabbits.

2. Materials and Methods

2.1. Chemicals

All chemicals were obtained commercially and were of analytical grade: Cholesterol (Mumbai India, M. W 386.67, CAS No. 57-88-5, LoT No. 100413) and Mega resveratrol: 99 % pure trans-resveratrol Batch Number: MR 131120, Average particle size: 2.5µm Sigma USA).

2.2. Equipments

Kits for blood glucose level determination digital glucometer (Accu-check advantage meter Cat No. 870, 50 test strips/code chip Cat No./item No. 049272/4900, Roche Diagnostic USA,). Electronic weighing scale Model: EK 3052 balance, dissecting set, syringes and middle (Sologuard Medical Device P.V.T Ltd., Chema-600 096, India, ML No. 750).

2.3. Experimental Animals

Seven weeks old male rabbits of different crossbreeds (New Zealand and local breed), weighing between 300 – 350 g raised in the Animal House, Department of Human Physiology Ahmadu Bello University Zaria, Nigeria were

used for the study. The animals were kept in well-aerated laboratory cages in the Departmental Animal House, and were allowed to adjust to the laboratory conditions for a period of three weeks before the commencement of the experiment. They were fed with growers' and starters' mash (Vital Feeds Company Kaduna, Nigeria) and water were provided during the stabilizing period.

2.4. Induction of Diabetes Mellitus

The normal groups were fed with standard animal feeds only, while the high fat diet groups were fed with standard animal feeds + Cholesterol diet (10% Groundnut oil, 20% Groundnut mill and 2% cholesterol/kg/day) for the induction diabetes mellitus for the experimental period which lasted for eight weeks.

2.5. Resveratrol Preparation and Administration

Trans-resveratrol, due to its low solubility in water, was suspended in 10 g/L of carboxymethylcellulose (CMC), and administered orally according to the method of [18]

2.6. Ethical Approval

The rabbits were handled in accordance with the principles guiding the use and handling of experimental animals Ahmadu Bello University, Zaria, Nigeria.

2.7. Groupings

In the study, 30 rabbits weighing between 300 and 350 g were used, each group comprised five rabbits (n = 5). The experiment lasted for 8 weeks. The groupings were as follows:

Group 1: Received 10 g/L CMC each orally (C)

Group 2: Receive high fat diet as feed only (HFD)

Group 3: Received 200 mg/kg body weight of resveratrol orally (R200 mg/kg).

Group 4: Received 400 mg/kg body weight of resveratrol orally (R400 mg/kg).

Group 5: Received 200 mg/kg body weight of resveratrol and cholesterol diet (R200 mg/kg + HFD).

Group 6: Received 400 mg/kg body weight of resveratrol and cholesterol diet (R400 mg/kg + HFD) [19].

2.8. Blood Glucose Level Determination

Blood samples were collected from the marginal vein ear lobe of the rabbits at an interval of eight weeks on weekly bases. Determination of blood glucose level was done by the glucose-oxidase principle [20], using the digital glucometer (Accu-Check Advantage, Roche Diagnostic, Germany), and results were obtained as mg/dL [21].

2.9. Collection and Preparation of Serum Samples for Analysis

Eight weeks after the treatment period, all rabbits were subjected to light anaesthesia by exposing them to chloroform soaked in cotton wool placed in anaesthetic box covered with lid. Blood samples of about 3 ml were drawn from the heart of

each sacrificed animal from all groups by cardiac puncture. The blood sample was put in EDTA bottle to prevent clotting, after with serum was extracted to determine the hormonal level of thyroid hormone.

2.10. Estimation of Serum T_3 and T_4 levels

Thyroid profile was estimated by using the enzyme-linked immunosorbent assay (ELISA) kits (T_3 and T_4) from sython Bioresearch, Inc, USA. thyroid hormone kit. T_3 were estimated according to [22]. T_4 were estimated according to [23]. The thyroid function was evaluated by determining the serum concentration of (T_3 and T_4) with a sensitivity of 20ng/L

2.11. Statistical Analysis

Blood glucose levels were expressed in mg/dL as mean \pm SEM. The data were analyzed using ANOVA followed by Dunett's *post-hoc* test to show multiple comparisons versus control group. Values of $P < 0.05$ were considered as significant [24].

3. Results

3.1. Blood Glucose Levels of Resveratrol Co-Administered with High Fat Diet Fed Rabbits

Table 1: shows the results of the effects resveratrol 200 mg/kg and 400 mg/kg of co-administered with high fat diet-fed rabbits, High fat diet-fed only, normal treated group and untreated group. The high fat diet fed rabbits showed significant ($P < 0.05$) increased in the blood glucose levels after 5 weeks of administration when compared to resveratrol treated group and normal control group. At 8 weeks of the experiment, HFD showed significant ($P < 0.05$) increase in blood glucose level with a value of 157.00 ± 14.47 mg/dL compared to HFD treated with resveratrol with decrease values of 119.00 ± 1.18 mg/dL for R200 + HFD and 110.20 ± 8.09 mg/dL for R400 + HFD respectively. The two doses of the resveratrol co-administered with high fat diet treated group significantly protect rise in blood glucose level when compared with the high fat diet only.

Table 1. Blood glucose levels of resveratrol co-administered with high fat diet fed rabbits for eight weeks of experimental period.

Group(n=5) (mg/dL)	WK 0	WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8
Control	110.40 \pm 8.87	121.40 \pm 3.01	125.80 \pm 2.60	114.00 \pm 7.93	119.80 \pm 4.19	125.40 \pm 2.50	110.00 \pm 3.24	119.80 \pm 10.44 ^a	120.00 \pm 7.07 ^a
R200	112.00 \pm 5.01	116.60 \pm 4.38	117.00 \pm 4.67	115.00 \pm 4.11	112.00 \pm 5.24	112.00 \pm 3.56	113.80 \pm 4.84	113.40 \pm 7.01	119.20 \pm .41
R400	108.00 \pm 2.43	117.80 \pm 2.04	116.40 \pm 1.97	105.00 \pm 2.41	117.80 \pm 3.38	114.60 \pm 3.30	117.00 \pm 3.33	97.80 \pm 2.33 ^c	105.60 \pm 2.73
HFD	107.40 \pm 4.46	119.00 \pm 5.15	101.40 \pm 6.68	110.80 \pm 3.84	113.60 \pm 4.49	121.80 \pm 3.60 ^b	135.60 \pm 3.71 ^b	135.00 \pm 14.29 ^b	157.00 \pm 14.47 ^b
HFD+ R200	97.40 \pm 4.65	112.80 \pm 3.65	106.60 \pm 5.81	108.40 \pm 6.17	110.60 \pm 2.91	101.40 \pm 5.03 ^a	110.60 \pm 5.16 ^a	122.80 \pm 3.34 ^a	119.00 \pm 1.18 ^a
HFD+R400	96.80 \pm 4.39	107.00 \pm 3.87	101.00 \pm 8.70	97.60 \pm 7.70	100.20 \pm 4.12	99.40 \pm 4.14 ^a	111.40 \pm 6.53 ^a	116.20 \pm 11.55 ^a	110.40 \pm 8.09 ^a

Values are expressed as mean \pm SEM; n = 5 Value considered statistically when compared with HFD group: a = $p < 0.05$ significant wk = week of administration. Values with error bars having different superscripts letters are significant ^{a,b,c}, = $p < 0.05$ significant

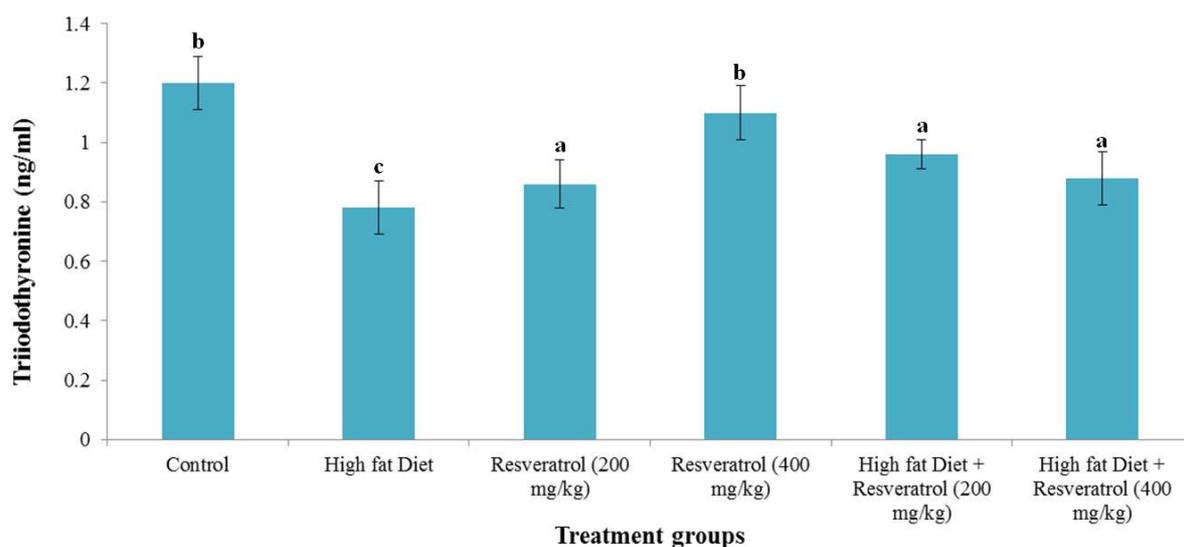


Figure 1. Effect of co-administration of resveratrol and high-fat diet on serum T_3 level in rabbits as compared with fed and unfed control group. Values are expressed as mean \pm SEM; n = 5 Values with error bars having different superscripts letters are significant ^{a,b,c}, = $p < 0.05$ significant.

Figure 1 shows serum level of T_3 in the group given resveratrol co-administered with HFD, resveratrol treated group alone and HFD group only. The result shows a significant ($P < 0.05$) decrease in T_3 level in HFD group with a value of 0.78 ± 0.09 ng/ml when compared to control group with an increase value of 1.2 ± 0.09 ng/ml. The values recorded for resveratrol co-administered with high fat diet were 0.96 ± 0.05 ng/ml and 0.88 ± 0.09 ng/ml which also shows significant ($P < 0.05$) increase when compared with HFD group with a value of 0.78 ± 0.09 ng/ml.

Figure 2 shows serum level of T_4 in the resveratrol

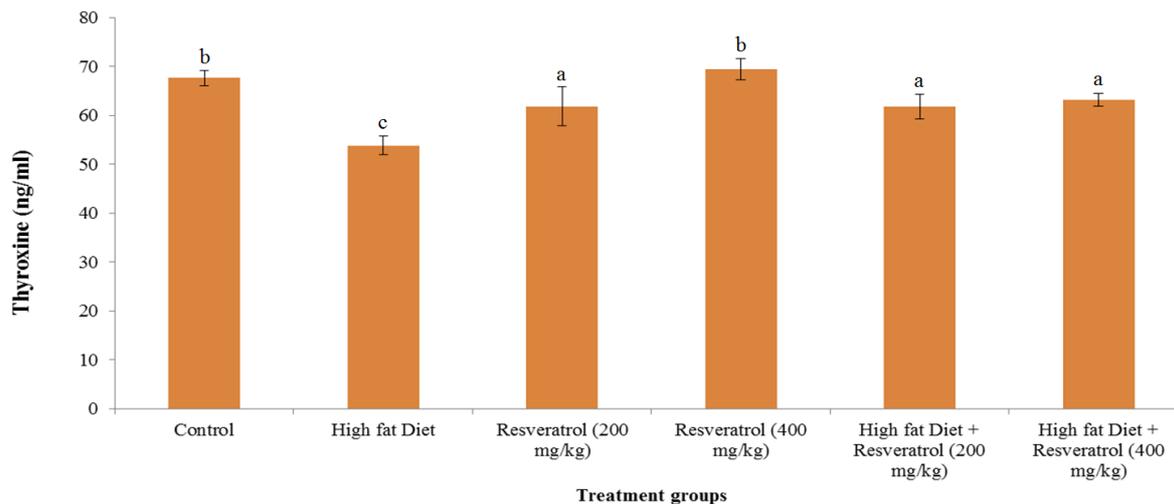


Figure 2. Effect of co-administration of resveratrol and high-fat diet on serum T_4 level in rabbits as compared with fed and unfed control group. Values are expressed as mean \pm SEM; $n = 5$. Values with error bars having different superscripts letters are significant $^{a,b,c} = p < 0.05$ significant.

4. Discussion

The highly predictive of new-onset T2DM is the presence of the metabolic syndrome (MetS) which increases the risk of T2DM [25,26]. T2DM is a complex disease caused by both environmental and genetic factors. It is marked by chronically elevated blood glucose concentrations, which result from defects in insulin production, insulin action, or a combination of both [27,28]. The aim of the present studies was to investigate the protective effect of resveratrol on blood glucose level and thyroid function of high fat diet-fed and unfed rabbits. In the present studies, the observed significant ($P < 0.05$) increase, in the blood glucose level in HFD group after 5 weeks of experimental protocol when compared to high fat diet groups treated with resveratrol indicates dysregulation in lipid metabolism. It is well known that a fat-enriched diet leads to the accumulation of adipose tissue and to the development of metabolic alterations associated with weight gain and diabetes mellitus [29]. Resveratrol has been shown to improve insulin sensitivity and lowers body weight in rodent models of diet-induced obesity, which leads to the speculation about its potential as an anti-diabetic in humans [30]. The presence of polyphenol in resveratrol has been postulated to inhibit intestinal absorption of glucose and increase bioavailability of insulin, by stimulating secretion of insulin from β -cells are some of the way which it exert

co-administered with HFD groups, resveratrol treated groups alone and HFD group only. The values recorded for resveratrol co-administered with high fat diet R200 + HFD = 61.80 ± 2.52 ng/ml and R400 + HFD = 63.20 ± 1.28 ng/ml showed a significant ($P < 0.05$) increase, when compared to the decrease value observed in HFD group only with a value of 53.80 ± 1.88 ng/ml respectively. With respect to control group, the control group also shows significant ($P < 0.05$) increase in T_4 level with a value of 67.60 ± 1.54 ng/ml when compared to the HFD only.

hypoglycaemic effect [31,32,33].

Stimulation of the activities of sirtuin 1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK) has demonstrated the anti-diabetic properties of resveratrol, and animals that lack AMPK fail to exhibit many of the normal responses to resveratrol [34,35]. The result of the present study is in agreement with the finding of [36], who demonstrate the hypoglycemic effect of resveratrol in enhancing insulin secretion in beta cells. The significant ($P < 0.05$) decrease observed in T_3 and T_4 level in HFD group compared to HFD + resveratrol indicate a state of hypothyroidism which impaired glucose oxidation and glycogen synthesis due to down-regulation of glucose transporter GLUT5 in humans and impaired GLUT4 transporter in animal model [7]. The result of the present study agreed with the finding of [7], who demonstrated the frequency of thyroid dysfunction among diabetes peoples. Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism. Excess or deficit of any one can result in functional derangement of the other [7]. The observed decrease in T_3 and T_4 may be as a result of hyperglycemia observed in the HFD group only. Diabetes mellitus has been known to impair thyroid metabolism. At low insulin sensitivity, minor change in TSH levels is associated with marked changes in lipid risk factors and, thus, cardiovascular risk [37]. The observed decrease in

blood glucose level and increase serum levels of T₃ and T₄ in HFD groups treated with resveratrol indicates protective effect of resveratrol against these disorders, since thyroid hormone have been known to stimulate thermogenesis, which is important in causing browning of white adipose tissue—a mechanism that burn, off excess fat in the body and improves glucose homeostasis [38,39].

5. Conclusion

High fat diet induced oxidative stress in rabbits, resulting in impairment of glucose metabolism and thyroid functions which was mitigated by resveratrol administration.

Acknowledgement

The authors wish to thank Mal Balla and ya'u technical staff of the Department of Human Physiology, Ahmadu Bello University Zaria, Nigeria. For their assistance throughout the period of this research work.

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