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Adropin and irisin levels in a rat model of hypothyroidism

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No available data exists about the relation of adropin and irisin levels and body weight in hypothyroidism. This work was designed to investigate the relationship between irisin and adropin levels and thyroid hormones. 40 male rats were divided into 2 groups: Control (C) group (10 rats) and hypothyroid group (30 rats). After induction of hypothyroidism, 18 rats increased in body weight (Hypothyroid overweight HO) and 12 rats did not show any significant weight gain (hypothyroid with normal body weight) (HNBW). Body mass index (BMI), adropin, irisin, T3, T4, and TSH were measured. Total cholesterol (TC), triglycerides (TG), serum HDL and LDL levels were estimated. Significant reductions were found in adropin and irisin levels in HO group compared with C and HNBW groups ($p<0.001$). T3 and T4 were significantly reduced in HO and HNBW groups compared with C group ($p<0.001$). Significant negative correlations were found between adropin, irisin levels (r=- 0.7967 and -0.7944, respectively) and BMI. Significant ($p < 0.01$) positive correlations were found between adropin (r=0.7095), irisin (r=0.711) and T3. Significant ($p < 0.01$) negative correlations were found between adropin and VLDL, TG, TC and LDL (r= -0.968, -0.966, -0.953 and -0.945, respectively) and positively correlated with HDL (r=0.415). Also, irisin was found to be negatively correlated with TG, TC, LDL and VLDL (r=-0.9251, -0.8579, -0.9688 and -0.9769, respectively) and positively correlated with HDL (r=0.5526). Reductions in adropin and irisin levels might be a part of overweight production observed in hypothyroidism.**

Key words: Adropin, hypothyroidism, body mass index, irisin, weight gain.

INTRODUCTION

Adropin, a secreted protein identified in 2008, is primarily expressed in the liver (Kumar et al., 2008). Reduced adropin levels in obesity were associated with metabolic derangements including pronounced insulin resistance, adiposity in liver and dyslipidemia (Ganesh et al., 2012). In addition, adropin was found to increase glucose utilization and decrease insulin level in obesity and diabetes type 2 (Akcilar et al., 2016). There is a negative correlation between adropin levels and incidence of metabolic syndrome, fatty liver, gestational diabetes mellitus and polycystic ovary syndrome (Beigi et al., 2015; Yosaee et al., 2017; Sayın, 2014; Kume et al., 2016). Low levels of plasma adropin were reported in diabetic patients (Wu et al., 2014). The relationship of

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adropin with energy regulation was confirmed by experimental evidence (Aydin, 2014).

Irisin is a peptide produced mainly by skeletal muscles and to a lesser extent other tissues like adipose, pancreatic tissues, sebaceous glands, and cardiac myocytes (Martinez Munoz, 2018). Irisin was related to anthropometric parameters finding differences in many studies (Moreno et al., 2015). Irisin was found to induce white adipose tissue browning, increase energy expenditure and transmit messages between skeletal muscle and endocrine glands (Panati et al., 2016; Boström et al., 2012).

Thyroid hormone is an essential determinant of energy regulation (Humerah et al., 2016). Adipose tissue hormones inform the CNS about the quantity of energy stores influencing the activity of the hypothalamo-pituitary-thyroid axis (Laurberg et al., 2012). Increased body weight in hypothyroid patients was reversed by thyroid hormone therapy (Baron, 1956). However, reduction in body weight was primarily attributed to a decrease in the fat free mass (Kyle et al., 1966). One of the main clinical features of thyrotoxicosis is weight loss (Johnson, 1919). Trials of using thyroid hormones in treatment of obesity in euthyroid subjects were done to stimulate energy expenditure (Biondi, 2010). A direct relationship between thyroid hormone levels and obesity' has been hypothesized (Rotondi et al., 2011; Pearce, 2012; Duntas and Biondi, 2013).

No available data about the relation of adropin and irisin levels exists in hypothyroid patients. It was postulated that irisin and adropin might play a role in weight gain occurring in hypothyroidism. This work was designed to investigate the relationship between irisin and adropin levels and hypothyroidism and to explore the correlation between changes in irisin and adropin levels and body weight gain observed during hypothyroidism.

MATERIALS AND METHODS

Albino rats (40 male; weighing 180-220 g) were divided into 2 groups; control group (10 rats) and hypothyroid group (30 rats) were allowed to free access to water and rat food for one week for acclimatization. Rats were kept in standard conditions of temperature and humidity (temperature 24 ± 3°C; humidity 25 ± 3%; 12 h light/dark cycle). All animal experiments were conducted in accordance with Helsinki Declaration Guide for the Care and Use of Laboratory Animals. Experimental protocol was approved by institutional ethics committee of Faculty of Medicine, Zagazig University (No. 441/2019/57).

Induction of hypothyroidism

Rats were given 0.05% of 6-propyl-2-thiouracil (PTU, Sigma) in drinking water for 20 days (Cortés et al., 2012; Legrand, 1967). Control group (10 rats) drink plain water. After induction of hypothyroidism, 18 rats increased in body weight (Hypothyroid overweight, HO) and 12 rats did not show any significant weight gain (hypothyroid with normal body weight, HNBW). After two weeks of established hypothyroidism (confirmed by measuring T3, T4 and TSH), the animals were injected sodium pentobarbital (30 mg/kg) i.p., then 3 mL of blood were collected from orbital fossa of each rat and centrifuged at 3000 rpm for 15 min. Levels of thyroid hormones T3, T4, and TSH were measured using Rat Thyroid Hormone kits (sigma Co., Cairo, Egypt) (Liu et al., 2019). Irisin is measured by ELISA kits (Rat Irisin ELISA kit, Sigma Co., Cairo, Egypt) (Kim et al., 2015). Adropin concentration was determined by commercial ELISA kits (Sigma Co., Egypt). Total cholesterol (TC), triglycerides (TG) and serum HDL levels were estimated according to Tietz (1995), Fossati and Prencipe (1982), and Nauck et al. (1997), respectively and LDL levels were calculated according to Friedewald et al. (1972). BMI was calculated simply by measuring body weight and dividing it over the square of length for all rats:

$$BMI = Body\ Weight/(Lenghth)^2$$

Statistical analysis

The data were expressed as mean ± SD. Unpaired T test was used to compare means between HO and C groups then between HNBW and C groups. Unpaired T test was also used to compare between HO and HNBW groups. Statistical analysis is performed by Graphpad Quickcalcs software. P value < 0.05 was considered statistically significant. Pearson correlation coefficient was used to measure the strength of linear association between the studied variables.

RESULTS

Table 1 shows that adropin decreased significantly from 5.36 ± 0.14 to 3.23 ± 0.12 and irisin levels from 1.4±0.03 to 0.8±0.02 in control and overweight hypothyroid groups, respectively ($p<0.001$). In addition, adropin decreased significantly from 5.25 ± 0.13 to 3.23 ± 0.12 and irisin levels from 1.4±0.02 to 0.8±0.02 in HNBW and HO groups, respectively ($p<0.001$).

Also, T3 and T4 were significantly reduced in overweight hypothyroid (T3, 47.37 ± 1.13 and T4, 0.53 ± 0.08) as well as normal weight hypothyroid (T3, 48.15 ± 1.14 and T4, 0.51 ± 0.07) groups compared with control group (T3, 86.16 ± 2.18 and T4, 1.46 ± 0.13) ($p<0.001$). TSH was significantly increased in hypothyroid groups (23.41 ± 2.13) compared with control (4.37 ± 1.12) group ($p<0.001$).

BMI was significantly ($p<0.001$) increased in overweight hypothyroid group (29.2 ± 2.1) compared with control (23.2 ± 2.3) and normal weight groups (24.2 ± 2.4).

Insignificant ($p>0.05$) changes were found in adropin (5.25 ± 0.13) and irisin (1.4±0.02) concentrations in normal weight hypothyroid group in comparison with control group (adropin, 5.36 ± 0.14 and irisin, 1.4±0.03). We did not find any significant differences in T3, T4 and TSH between the two hypothyroid groups (HO: T3, 47.37 ± 1.13; T4, 0.53 ± 0.08; TSH, 23.41 ± 2.13; NBWG, T3, 48.15 ± 1.14; T4, 0.51 ± 0.07; TSH, 24.25 ± 2.14).

Table 2 shows that total cholesterol, triglycerides, LDL and VLDL are significantly higher ($p<0.001$) in overweight hypothyroid group (Tc, 1.95 ± 0.05; TG, 1.06 ± 0.17; LDL, 47.63 ± 1.73; VLDL, 14.19 ± 0.44) in comparison with control (Tc, 0.97 ± 0.08; TG, 1.06 ± 0.17; LDL, 1.11 ± 0.29; VLDL, 14.19 ± 0.44) and normal weight (Tc, 1.02 ±

Table 1. Hormonal profile (values presented as Mean ± SD).

Profile (ng/ml)	Control group (C)	Overweight Hypothyroid group (HO, n=18)	Normal weight Hypothyroid group (HNBW, n=12)
Adropin	5.36 ± 0.14	3.23 ± 0.12^{a}***	5.25 ± 0.13$^{a\#}$, ^{b}**
Irisin	1.4±0.03	0.8 ± 0.02^{a}***	1.4 ± 0.02$^{a\#}$, ^{b}**
T3	86.16 ± 2.18	47.37 ± 1.13^{a}***	48.15 ± 1.14^{a}***, $^{b\#}$
T4	1.46 ± 0.13	0.53 ± 0.08^{a}***	0.51 ± 0.07^{a}***, $^{b\#}$
TSH	4.37 ± 1.12	23.41 ± 2.13^{a}***	24.25 ± 2.14^{a}***, $^{b\#}$
BMI	23.2 ± 2.3	29.2 ± 2.1^{a}***	24.2 ± 2.4$^{a\#}$, ^{b}**

a=in comparison with control group; b=in comparison with HO group. *Significant ≤0.05, ***Significant ≤0.05, $^{\#}$Non-significant >0.05.

Table 2. Lipid profile (values presented as Mean ± SD).

Profile	Control group (C)	Overweight hypothyroid group (HO)	Normal weight hypothyroid group (HNBW)
Total cholesterol (TC)	0.97 ± 0.08	1.95 ± 0.05^{a}***	1.02 ± 0.05$^{a\#}$, ^{b}**
Triglycerides (TG)	1.06 ± 0.17	1.88 ± 0.23^{a}***	1.07 ± 0.19$^{a\#}$, ^{b}**
HDL-c	1.11 ± 0.29	0.76 ± 0.21^{a}**	1.12 ± 0.33$^{a\#}$, ^{b}**
LDL-c	47.63 ± 1.73	77.51 ± 1.55^{a}***	48.55 ± 1.67$^{a\#}$, ^{b}***
VLDL	14.19 ± 0.44	17.12 ± 0.35^{a}***	14.11 ± 0.43$^{a\#}$, ^{b}**

a=in comparison with control group; b=in comparison with HO group. *Significant ≤0.05, ***Significant ≤0.05, $^{\#}$Non-significant >0.05

Table 3. Correlation between adropin and BMI.

Profile	Control group (C)	Overweight hypothyroid group (HO)	Normal weight hypothyroid group (HNBW)
Adropin	5.36 ± 0.14	3.23 ± 0.12	5.02 ± 0.13
BMI	23.2 ± 2.3	29.2 ± 2.1	24.2 ± 2.4
r		-0.7967***	

***Strong negative correlation= highly significant ≤0.05. **r=** Pearson correlation coefficient.

0.05; TG, 1.07 ± 0.19; LDL, 48.55 ± 1.67; VLDL, 14.11 ± 0.43) hypothyroid groups.

A significant (p>0.05) reduction in HDL was found in overweight group (0.76 ± 0.21) compared with control (1.11 ± 0.29) and normal weight hypothyroid (1.12 ± 0.33) groups. Insignificant differences in serum lipids were found in normal weight hypothyroid group compared with controls.

Table 3 shows strong negative correlations between adropin, irisin levels (r=- 0.7967** and -0.7944, respectively) and body mass index. Table 4 shows that adropin was positively correlated (r=0.7095) with T3 (p<0.05). Table 5 shows that irisin levels were negatively correlated with body mass index (r= -0.7944, p<0.05). Table 6 shows significant (p < 0.01) positive correlations between irisin (r=0.711) and T3. Table 7 shows significant (p < 0.01) negative correlations were found between adropin and VLDL, TG, TC and LDL (r = -0.968, -0.966, -0.953 and -0.945, respectively) and positively correlated with HDL (r=0.415). Also, irisin was found to be negatively correlated with TG, TC, LDL and VLDL (r=-0.9251, -0.8579, -0.9688 and -0.9769 respectively) and positively correlated with HDL (r=0.5526).

DISCUSSION

Irisin a myokine induces browning of white adipose tissue and increases energy expenditure promoting weight loss (Zhang et al., 2014). *In vitro*, irisin added to mouse primary adipocytes increased thermogenic genes and energy consumption (Martinez et al., 2018). So, we postulated that weight gain occurring in hypothyroidism might be attributed to irisin reductions and other hormonal changes.

Adropin is a powerful regulatory hormone of insulin

Table 4. Pearson correlation between adropin and T3.

Profile	Control group (C)	Overweight hypothyroid group (HO)	Normal weight hypothyroid group (HNBW)
Adropin	5.36 ± 0.14	3.23 ± 0.12	5.02 ± 0.13
T3 (ng/mL)	86.16 ± 2.18	47.37 ± 1.13	45.33 ± 1.14
r		0.7095**	

**Significant p ≤0.05. r= Pearson correlation coefficient.

Table 5. Pearson correlation between irisin and BMI.

Profile	Control group (C)	Overweight hypothyroid group (HO)	Normal weight hypothyroid group (HNBW)
Irisin (ng/ml)	1.4 ± 0.03	0.8 ± 0.02	1.3 ± 0.02
BMI	23.2 ± 2.3	29.2 ± 2.1	24.2 ± 2.4
r		-0.7944*** (strong negative correlation)	

***Highly significant ≤0.05. r=Pearson correlation coefficient.

Table 6. Pearson Correlation between Irisin and T3.

Profile	Control group (C)	Overweight hypothyroid group (HO)	Normal weight hypothyroid group (HNBW)
Irisin (ng/ml)	1.4 ± 0.03	0.8 ± 0.02	1.3 ± 0.02
T3 (ng/ml)	86.16 ± 2.18	47.37 ± 1.13	45.33 ± 1.14
r		0.711**	

** Significant ≤0.05. r=Pearson correlation coefficient.

sensitivity and energy homeostasis (Zang et al., 2018). Butler et al. (2019) reported that weight gain occurred in animals with low adropin and high leptin.

Hypothyroidism is a well-known disease of insufficient thyroid hormones (Aiceles and De Fonte, 2016). Thyroid hormone is an essential determinant of energy regulation (Humerah et al., 2016). Adipose tissue hormones inform the CNS about the quantity of energy stores influencing the activity of the hypothalamo-pituitary-thyroid axis (35). The exact cause and mechanism of weight gain associated with hypothyroidism is a complex process involving interaction between thyroid and other hormones. No available data demonstrated the relationship between adropin and irisin on one hand and weight gain during hypothyroidism on the other hand. According to available data, this study is the first to examine the association between irisin and adropin concentrations and BMI in hypothyroidism.

In this study, induction of hypothyroidism results in weight gain in 18 rats out of 30 (60%) and did not cause any significant weight gain in 12 rats (40%). These events are consistent with the reports of Humerah et al. (2016) who reported that 54% of hypothyroid patients gain weight. Weight gain occurring in hypothyroidism might be attributed to accumulation of fat and physical inactivity (Seppel et al., 1997; Wolf et al., 1996; Smith et al., 1989). Monitoring of hypothyroidism treatment is best done by lean body mass (Santini et al., 2005).

The present study found significant reductions in adropin and irisin levels in overweight hypothyroid group compared with control and normal weight hypothyroid group ($p<0.001$). These findings are supported by Majeed et al. (2019) who found that irisin significantly lowers the elevated BMI and serum insulin levels in female mice. We suggested that increased weight observed in group 2 (overweight hypothyroid) might be attributed to this reduction in adropin and irisin levels. Our suggestion and findings are in line with Niranjan et al. (2019) who found that irisin reduced body weight, insulin and lipids in obese mice. Our results were also in agreement with Zhou et al. (2016) who found that low plasma irisin level was associated with obesity and insulin resistance, which were improved after irisin administration. Thus, irisin was considered as a potential therapeutic target for obesity and some metabolic disorders (Liu et al., 2019). Our findings were also supported by Zang et al. (2018) who found significant reductions in adropin concentrations in T2DM patients, especially overweight and/or obese. Our

Table 7. Pearson correlation between adropin, irisin and serum lipids.

Profile	VLDL	TG	TC	LDL	HDL
Adropin	-0.968*** Strong negative correlation	-0.966*** Strong negative correlation	-0.953*** Strong negative correlation	-0.9457*** Strong negative correlation	0.4158# Weak +ve correlation
Irisin	-0.9251*** Strong negative correlation	-0.8579*** Strong negative correlation	-0.9688*** Strong negative correlation	-0.9769*** Strong negative correlation	0.5526* (p=0.01) Moderate +ve correlation

*Significant correlation ≤0.05. ***Highly significant correlation ≤0.05.

findings were also in line with previous studies that reported administration of irisin to obese mice improved glucose tolerance and reduced body weight (Zhang et al., 2014).

In this study, T3 and T4 were significantly reduced in overweight hypothyroid as well as normal weight hypothyroid groups compared with control group (p<0.001). These findings are in agreement with Aiceles et al. (2016) who reported an increase in body weight in hypothyroid patients.

In the current study, TSH was significantly increased in hypothyroid groups compared with control group (p<0.001). Our results were supported by studies that reported a higher prevalence of elevated TSH in obese children compared with controls and levels of TSH normalize after substantial weight loss (Humerah et al., 2016). These findings are also in line with Iacobellis et al. (2005) who found higher serum TSH in obese women with BMI >40 more than those below 40 (P < 0.01). They concluded that TSH is correlated with leptin suggesting that TSH might be a marker of disturbed energy homeostasis in severe obese women. Our results are also in line with other studies suggesting that obesity per se is associated with moderately elevated TSH levels in association with normal or slightly elevated Free T4 and/or Free T3 levels (Reinehr, 2011) as we found that TSH is elevated in both groups of hypothyroidism regardless of the weight; so the weight change must be attributed to other mechanisms as was suggested in this study.

In the present study, BMI was significantly increased in overweight hypothyroid group compared with control and normal weight groups (p<0.001). These results are in agreement with Tomer and Davies (2003) who reported that obesity and autoimmune thyroid disease depends mainly on genetic determinants. The findings of our study were also in line with observational data suggesting that obesity may increase the risk of several autoimmune diseases, possibly from the accumulation of adipose tissue in obese patients (Hersoug and Linneberg, 2007; Procaccini et al., 2011). We suggested that reductions in adropin and leptin in hypothyroidism may be a part of overweight production. Our suggestion was in line with Wang et al. (2009) who reported that leptin influenced T regulatory cells involved in the control of autoimmunity and of thyroid cell apoptosis. Our results are in controversy with Liu et al. (2019) who did not find significant correlation between irisin and baseline BMI and weight but this controversy may be due to the small sample size of each subgroup in their study. However, in the longitudinal study, they found a negative correlation between irisin level and BMI. Our findings are also in agreement with other studies reporting that higher baseline irisin was associated with a greater reduction in body weight (Lopez-Legarrea et al., 2014). Our findings were also in line with Santini et al. (2005) who reported an association between hypothyroidism and weight gain.

In the present study, insignificant changes were found in adropin and irisin concentrations in normal weight hypothyroid group in comparison with control group (p>0.05). Not significant differences were found in T3, T4 and TSH between the two hypothyroid groups (p>0.05) which confirmed our suggestion of hormonal factors other than thyroid hormones which resulted in weight gain during hypothyroidism. This hormonal factor might be attributed to adropin and irisin.

In the present study, total cholesterol, triglycerides, LDL and VLDL increased significantly in overweight hypothyroid group in comparison with control and normal weight hypothyroid groups (p<0.001). A significant reduction in HDL was found in overweight group compared with control and normal weight hypothyroid groups. Insignificant differences in serum lipids were found in normal weight hypothyroid group compared with controls (p>0.05). These findings are consistent with Humerah et al. (2016) who found a significant elevated lipids in hypothyroid

patients compared with the euthyroid subjects ($p < 0.05$) and significant correlation of lipid profile with the BMI ($p < 0.01$). Our findings were also in line with Zang et al. (2018) who found significant reductions in adropin concentrations in T2DM patients, especially overweight and/or obese.

In present study, strong negative correlations were found between adropin, irisin levels (r=- 0.7967 and -0.7944, respectively) and body mass index. These results are in agreement with Zang et al. (2018) who found a negative correlation between adropin and body mass index (BMI) ($p < 0.01$). Our findings were in controversy with Huh et al. (2012) who found a positive correlation between irisin and BMI in adult women. This controversy might be attributed to the small sample (18 subjects) in cross sectional study. Our results were in agreement with Moreno-Navarrete et al. (2015) who found lower FNDC5 expression in obese Caucasians in skeletal muscle and adipose tissue, as well as decreased serum irisin level. Our data are consistent with the findings of Butler et al. (2019) who concluded that low adropin levels predict weight gain and metabolic derangements.

Our findings were also in agreement with Choi et al. (2013) who found a negative correlation between serum irisin and BMI. The latter findings were also reported by Klangjareonchai et al. (2014).

In the present study, significant ($p < 0.01$) positive correlations were found between adropin (r=0.7095), irisin (r=0.711) and T3. These findings are in line with Iacobellis et al. (2005) who found that TSH was negatively correlated with BMI, leptin, HOMA-IR and they concluded that TSH might be used as a marker of disturbed energy homeostasis in severe obese women. Our findings are also in consistent with Aiceles and da Fonte Ramos (2016) who reported an inverse correlation between free thyroxin values and body mass index.

In the present study, significant ($p < 0.01$) negative correlations were found between adropin and VLDL, TG, TC and LDL (r= -0.968, -0.966, -0.953 and -0.945, respectively) and positively correlated with HDL (r=0.415). Also, irisin was found to be negatively correlated with TG, TC, LDL and VLDL (r=-0.9251, -0.8579, -0.9688 and -0.9769, respectively) and positively correlated with HDL (r=0.5526). These findings are in agreement with Zang et al. (2018) who found that adropin level was negatively correlated with triglycerides (TG) and HOMA2-IR, and positively correlated with HDL ($p < 0.01$).

Conclusions

The present study found significant reductions in adropin and irisin levels in overweight hypothyroid group compared with control and normal weight hypothyroid group ($p<0.001$). T3 and T4 were significantly reduced in overweight hypothyroid as well as normal weight hypothyroid groups compared with control group ($p<0.001$). TSH was significantly increased in hypothyroid groups compared with control group ($p<0.001$). Total cholesterol, triglycerides, LDL and VLDL increased significantly in overweight hypothyroid group in comparison with control and normal weight hypothyroid groups ($p<0.001$). A significant reduction in HDL was found in overweight group compared with control and normal weight hypothyroid groups. A strong negative correlations were found between adropin, irisin levels (r= -0.7967** and -0.7944, respectively) and body mass index. A significant ($p < 0.01$) positive correlations were found between adropin (r=0.7095), irisin (r=0.711) and T3. A significant ($p < 0.01$) negative correlations were found between adropin and VLDL, TG, TC and LDL (r= -0.968, -0.966, -0.953 and -0.945, respectively) and positively correlated with HDL (r=0.415). Also, irisin was found to be negatively correlated with TG, TC, LDL and VLDL (r=-0.9251, -0.8579, -0.9688 and -0.9769, respectively) and positively correlated with HDL (r=0.5526). It was concluded that reductions in adropin and irisin in hypothyroidism may be a part of overweight production. Weight gain associated with hypothyroidism might be attributed to adropin and irisin reductions apart from thyroid hormone deficiency.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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