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EVALUATION OF SERUM IRISIN AND CREATINE KINASE LEVELS IN HYPO- AND HYPERTHYROID RATS

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ABSTRACT

Background: Thyroid dysfunction is one of the most common metabolic disorders that has not been dependent yet in its diagnosis on evaluation of serum levels of thyroid stimulating hormone (TSH), tri-iodothyronine (T3), thyroxine (T4). Other markers like serum irisin which is an adipo-myokine secreted by muscles during exercise, and serum creatine kinase (CK) which is a marker of muscle damage, show changes in their levels with hypo and hyperthyroidism in different species.

Objective: To evaluate the levels of both serum irisin and serum creatine kinase in hypo- and hyperthyroid rats, and to illustrate the relationship between their levels and thyroid function tests.

Methods: This study was performed on 30 adult healthy male local strain albino rats that were divided into three equal groups: Group I (Control " Euthyroid" group): Fed on commercial rat laboratory chow, Group II (Hypothyroid group): Hypothyroidism was induced by administration of propylthiouracil, and Group III (Hyperthyroid group): Hyperthyroidism was induced by administration of T4. BMI in each group was calculated at the end of the experiment. Hormonal assay was performed to measure serum levels of TSH, FT3, FT4, insulin, glucose, irisin and CK.

Results: Serum irisin was negatively correlated with TSH levels, and positively correlated with FT3 and FT4 levels in both hypo-and hyperthyroid groups. However, serum CK was positively correlated with TSH levels and negatively correlated with FT3 and FT4 levels in both hypo-and hyperthyroid groups. Also, a negative correlation between serum irisin and serum CK was recorded in both cases of thyroid dysfunction.

Conclusions: Serum irisin level decreased in hypothyroid and increased in hyperthyroid rats. At the same time, serum CK level increased in hypothyroid and decreased in hyperthyroid rats. Both serum irisin and CK levels may be considered as parameters for diagnosis of both hypo-and hyperthyroidism in rats.

Key words: Irisin, Creatine Kinase, Thyroid dysfunction, Rats.

INTRODUCTION

Irisin is an adipo-myokine that is secreted by muscles during physical exercise, and has a significant influence on metabolism and thermogenesis, mostly by promoting browning of white adipose tissue **(Bostrom et al., 2012 and Zhang et al., 2014).** Also, thyroxine (T4) and metabolically active triiodothyronine (T3) increase heat production and control the energy balance by stimulating numerous metabolic pathways including the influence on brown adipose tissue **(Lanni et al., 2016).**

As a result of these similarities in action between irisin and thyroid

hormones, many researchers have tried to find a relationship between irisin and thyroid hormones levels in thyroid dysfunction **(Ruchala et al., 2014 and Zybek-Kocik et al., 2016).**

On the other hand, serum creatine kinase (CK) is considered as a clinical marker for progressive muscle damage as in cases of myocardial infarction, rhabdomyolysis and muscular dystrophy **(Brewster et al., 2012).** Musculoskeletal disorders are common in patients with hypothyroidism. These are also observed in thyrotoxicosis, and level of CK altered in both these conditions **(Samy et al., 2015)**. Studies have been established to evaluate a relationship of CK levels in thyroid disease **(Panag et al., 2012)**.

Thyroid dysfunction is considered one of the most common endocrine diseases that is associated with metabolic imbalance, abnormal energy homeostasis, oxidative stress and muscle disorders **(Alemu et al., 2016).**

In this study, we tried to find new diagnostic tools for diagnosis of hypo-and hyperthyroidism in rats as changes in serum irisin and serum CK levels. Also, we studied many relationships between both serum irisin and CK levels and different parameters in thyroid dysfunction.

MATERIALS AND METHODS

Animals: This study was performed on a total number of 30 adult male albino rats of local strain, (weighing 150 – 180 grams). Animals were kept under hygienic conditions in steel wire cages (٤٠ x28 x18 cm)**,** 5 rats per cage. in the animal house of the Faculty of Medicine Zagazig University. All rats had free access to water and commercial rat standard chow which consisted of 25.8% protein, 62.8% carbohydrates and 11.4% fat **(Ahren and Scheurink, 1998**). Rats were kept at comfortable temperature (20-24?C) and were maintained on a normal light/dark cycle **(Lesourd and Mazari, 1999**).

The rats were adapted to laboratory conditions for one week before starting the experimental regimen. All the experimental procedures were conducted in accordance with the guiding principles for the care and use of research animals.

Groups: The rats were divided into three equal groups:

1. Group I (Control or Euthyroid group) fed on normal standard diet

2. Group II (Hypothyroid group) in which experimental hypothyroidism was induced according to **Pantos et al. (2006)** by administration of propylthiouracil (50 mg/dl) (0.05%) in the drinking water for 3 weeks in the form of Thyrocil tablets. Each tablet contained 50 mg propylthiouracil (the drug was purchased from Amoun Pharmaceutical Co. S.A.E, Cairo A.R.E.).

3 - Group III (Hyperthyroid group) in which experimental hyperthyroidism was induced according to **Morovat and Dauncey (1998)** by administration of T4 600 µg/dl (6 x 10^{-4}%) in the drinking water for 3 weeks in the form of Eltroxin tablets. Each tablet contained 100µg thyroxine sodium (the drug was purchased from Glaxo Wellcome Egypt S.A.E, Cairo A.R.E.).

Hypo and hyperthyroidism were confirmed three weeks later by measuring serum thyroid-stimulating hormone

(TSH), triiodothyronine (T3), and thyroxine (T4) levels.

Blood samples were obtained at the time of scarification and were allowed to clot for 2 hours at room temperature and were centrifuged for 20 min. at approximately 500 rpm. The separated serums were stored at -20ºC **(Nishizawa et al., 2002),** until used for:

1. Estimation of serum thyroid stimulating hormone (TSH) levels (µIU/ml) by chemiluminescence immunoassay according to **Cardosi et al. (1989**), using Biotech TSH CLIA kit was purchased from Jei Daniel Biotech Corp. Inc., France.
2. Estimation of serum free tri-iodothyronine (FT3) levels (ng/ml) by radioimmunoassay according to **Larsen (1981).**
3. Estimation of serum free thyroxine (FT4) levels (µg/dl) by radioimmunoassay according to **Lethotaty et al. (1982).**

   Kits for estimation of both FT3&FT4 :(Elecsys D-68298 kits) were purchased from Mannheim, Germany.
4. Estimation of serum irisin levels (µg/ml) by using enzyme – linked immunosorbent assay (ELISA) according to **Ruchala et al. (2014**) using irisin competitive ELISA Kit (K4761-100). Biovision,Inc. Mountain View, California, U.S.A. Range of detection (0.001µg/ml - 5µg/ml).
5. Estimation of serum creatine kinase levels (CK) - (U/L) by using CK-NAC method, according to **Tejomani et al. (2013)** using creatine kinase C7522 kits. POINTE.SCIENTIFIC.U.S.A. Range of detection (1-1200 U/L).
6. Estimation of serum glucose levels (mg/dl) according to **Tietz (1995**).
7. Estimation of serum insulin levels (µIU/ml) by enzyme – linked immuno-sorbent assay (ELISA) according to **Reaven (1991).**

   Kits for estimation of serum glucose and insulin levels were purchased from (Biosource Europe S.A.Belgium).
8. Calculation of HOMA-IR: Insulin resis-tance (IR) of individual rats was evaluated using the homeostasis model assessment (HOMA-IR) index according to **Bonora et al. (2000**) as follows:

   [HOMA-IR] = fasting serum glucose (mg/dL) × fasting serum insulin (?IU/mL)/405.
9. Calculation of Body Mass Index (BMI) (gm/cm^2): The weights and lengths were measured at the end of their experiment, and immediately before they were sacrificed for calculation of the BMI. It can be calculated by dividing body weight (gm)/ $length^2$ (cm^2).

Weight was measured by using a digital scale in grams according to **Nascimento et al. (2008**) and Length was measured Nose to anus length was measured in cm. according to **Novelli et al. (2007**).

Statistical Analysis: The data obtained in the present study were expressed as mean ± SD for quantitative variables and statistically analyzed according to the methods described by **Kirkwood (1989**). The statistical analysis is done by using

SPSS program (19) (SPSS Inc. Chicago, IL, USA). P value < 0.05 was considered statistically significant.

ANOVA test was used to compare means among more than two groups. **Post hoc test (LSD)** was used for ANOVA test.

Corrélation coefficient (r): Pearson's correlation analysis was performed to screen potential factors related to serum concentrations of both irisin and creatine kinase. Test was considered significant at P values <0.05.

RESULTS

This study recorded a significant increase in serum TSH level (μIU/ml) in hypothyroid group (0.0113 ± 0.0019) when compared to control group (0.005 ± 0.0012) (P < 0.001) as well as significant decrease in its level in hyperthyroid group (0.0026 ± 0.0011) when compared to both control and hypothyroid groups (P < 0.01, P < 0.001 respectively).

At the same time, there was a significant decrease in serum FT3 level (ng/ml) in hypothyroid group (0.562 ± 0.153) when compared to control group (1.174 ± 0.121) (P < 0.001) as well as significant increase in its level in hyperthyroid group (3.406 ± 0.411) when compared to both control and hypothyroid groups (P < 0.001, P <0.001 respectively).

Also, there was a significant decrease in serum FT4 level (μg/dl) in hypothyroid group (0.928±0.155) when compared to control group (5.631±0.718) (P < 0.001) as well as significant increase in its level in hyperthyroid group (17.491±1.564) when compared to both control and hypothyroid groups (P< 0.001, P<0.001 respectively).

Significant decrease in serum irisin level (μg/ml) was detected in hypothyroid group (0.47±0.12) when compared to control group (1.42±0.15) (P < 0.001) as well as significant increase in its level in hyperthyroid group (3.16±0.57) when compared to both control and hypothyroid groups (P < 0.001, P<0.001 respectively).

On the other hand, there was a significant increase in serum CK level (U/L) in hypothyroid group (398.4±14.91) when compared to control group (152.3±8.38) (P < 0.001) as well as significant decrease in its level in hyperthyroid group (108.2±8.46) when compared to both control and hypothyroid groups (P < 0.001, P<0.001 respectively).

No significant changes in serum glucose level (mg/dl) in hypothyroid group (80.6±5.99) when compared to control group (85.4±7.55) (P > 0.05), but there was a significant increase in its level in hyperthyroid group (121.3±7.94) when compared to both control and hypothyroid groups (P < 0.001, P < 0.001 respectively).

This study observed no significant changes in serum insulin level (μIU/ml) in hypothyroid group (11.76±1.49) when compared to control group (12.45±1.58) (P > 0.05), but there was significant increase occurred in its level in hyperthyroid group (28.87±1.78) when compared to both control and hypothyroid groups (P < 0.001, P < 0.001 respectively).

There was no significant change in HOMA-IR value in hypothyroid group (2.34±0.22) when compared to control group (2.63±0.34) (P > 0.05), but there was a significant increase in its value in hyperthyroid group (8.65±0.56) when

compared to both control and hypothyroid groups (P < 0.001, P < 0.001 respectively).

Significant increase occurred in BMI (gm./cm^2) in hypothyroid group (0.58 ± 0.042) when compared to control group (0.44±0.058) (P < 0.001) as well as significant decrease in its value in hyperthyroid group (0.38±0.048) when compared to both control and hypothyroid groups (P <0.01,P< 0.01 respectively) (**Table 1**).

Table (1): Biochemical blood analysis and metabolic parameters in the three studied groups expressed as (mean ± SD).

Groups / Parameters	Group I (Euthyroid)	Group II (Hypothyroid)	Group III (Hyperthyroid)
Serum TSH (µIU/ml)	0.005±0.0012	0.0113±0.0019^{***a}	0.0026±0.0011^{**a,***b}
Serum Free T3 (ng/ml)	1.174±0.121	0.562±0.153^{***a}	3.406±0.411^{***a,b}
Serum FreeT4 (µg/dl)	5.631±0.718	0.928±0.155^{***a}	17.491±1.564^{***a,b}
Serum Irisin (µg/ml)	1.42±0.15	0.47±0.12^{***a}	3.16±0.57^{***a,b}
Serum CK(IU/L)	152.3±8.38	398.4±14.91^{***a}	108.2±8.46^{***a,b}
Serum Glucose (mg/dl)	85.4±7.55	80.6±5.99	121.3±7.94^{***a,b}
Serum Insulin(µIU/ml)	12.45±1.58	11.76±1.49	28.87±1.78^{***a,b}
HOMA-IR	2.63±0.34	2.34±0.22	8.65±0.56^{***a,b}
BMI (gm/cm^2)	0.44±0.058	0.58±0.042^{***a}	0.38±0.048^{**a,***b}

** = P < 0.01 *** = P < 0.001 a = versus group I b = versus group II

Significant negative correlation was recorded between serum irisin and TSH levels in both hypo-and hyperthyroid groups (r= -0.873**, P<0.01 & r= -0.987***, P<0.0001 respectively) as well as a significant Positive correlation between serum irisin and FT3 levels in both hypo- and hyperthyroid groups (r= 0.986***, P<0.001 & r= 0.981***, P<0.001 respectively) And also a Positive correlation between serum Irisin&FT4 levels in both hypo- and hyperthyroid groups: (r= 0.985***, P<0.001 & r= 0.974***, P<0.0001 respectively).

At the same time, there were no significant correlations recorded between serum irisin and TSH, FT3 or FT4 levels in the control group. Also, no significant correlations were recorded between serum irisin, BMI, serum glucose and insulin levels, or HOMA-IR in any of the three studied groups (**Table 2**).

Table (2): Correlations between serum irisin (μg/ml) levels and all studied parameters in all studied groups.

Groups / Parameters	Group I (Euthyroid)	Group II (Hypothyroid)	Group III (Hyperthyroid)
Serum TSH (μIU/ml)	r = 0.554 P > 0.05	r = - 0.873** P < 0.01	r = - 0.981*** P < 0.001
Serum Free T3 (ng/ml)	r = 0.327 P > 0.05	r = 0.970*** P < 0.001	r = 0.963*** P< 0.001
Serum Free T4 (μg/dl)	r = 0.357 P > 0.05	r = 0.966*** P < 0.001	r = 0.974*** P < 0.001
Serum CK (U/L)	r = 0.432 P > 0.05	r = - 0.987*** P < 0.001	r = - 0.845** P < 0.01
Serum Glucose (mg/dl)	r = 0.144 P > 0.05	r = 0.174 P > 0.05	r = 0.178 P > 0.05
Serum Insulin (μIU/ml)	r = 0.141 P > 0.05	r = 0.062 P > 0.05	r = 0.203 P > 0.05
HOMA-IR	r = 0.050 P > 0.05	r = 0.012 P > 0.05	r = 0.307 P > 0.05
BMI (gm/cm^2)	r = 0.338 P > 0.05	r = 0.006 P > 0.05	r = 0.104 P > 0.05

** = P < 0.01 *** = P < 0.001

There was a significant positive correlation between serum CK&TSH levels in both hypo-and hyperthyroid groups (r= 0.926***, P<0.001 &r= 0.989***, P<0.0001 respectively). Also, there was a significant negative correlation between serum CK and FT3 levels in both hypo-and hyperthyroid groups (r= -0.994***, P<0.001 & r= -0.969***, P<0.001 respectively) and significant negative correlation between serum CK and FT4 levels in both hypo- and hyperthyroid groups: (r = -0.972***, P< 0.001 &r = -0.976***, P < 0.001 respectively).

On the other hand, there was no significant correlation recorded between serum CK and TSH, FT3 or FT4 levels in the control group. At the same time, no significant correlations recorded between serum CK, BMI, serum glucose and insulin levels Or HOMA-IR in any of the three studied groups.

There was a significant negative correlation between serum irisin and CK level in both hypo-and hyperthyroid groups were detected: (r= -0.987***, P<0.001 and r= -0.845**, P<0.01 respectively). No significant correlations were recorded between serum irisin and CK levels in the control group (**Table 3**).

Table (3): Correlations between serum CK (U/L) levels and all studied parameters in all studied groups.

Groups / Parameters	Group I (Euthyroid)	Group II (Hypothyroid)	Group III (Hyperthyroid)
Serum TSH (µIU/ml)	r = 0.203 P > 0.05	r = 0.926*** P < 0.001	r = 0.989*** P < 0.001
Serum Free T3 (ng/ml)	r = 0.244 P > 0.05	r = - 0.994*** P < 0.001	r = - 0.969*** P< 0.001
Serum Free T4 (µg/dl)	r = 0.112 P > 0.05	r = - 0.972*** P < 0.001	r = - 0.976*** P < 0.001
Serum Irisin (µg/ml)	r = 0.432 P > 0.05	r = - 0.987*** P < 0.001	r = - 0.845** P < 0.01
Serum Glucose (mg/dl)	r = 0.144 P > 0.05	r = 0.048 P > 0.05	r = 0.178 P > 0.05
Serum Insulin (µIU/ml)	r = 0.405 P > 0.05	r = 0.027 P > 0.05	r = 0.020 P > 0.05
HOMA-IR	r = 0.111 P > 0.05	r = 0.063 P > 0.05	r = 0.179 P > 0.05
BMI (gm/cm^2)	r = 0.077 P > 0.05	r = 0.069 P > 0.05	r = 0.077 P > 0.05

** = P < 0.01 *** = P < 0.001

DISCUSSION

Changes in both serum irisin and serum CK levels in different cases of thyroid dysfunction were reported by many scientists **(Hekimosy & Oktem, 2005, Ruchala et al., 2014 and Samy et al., 2015).**

This study was performed to demonstrate the serum levels of both irisin and CK in hypo- and hyperthyroid rats. And also to illustrate the relationships between their levels and the thyroid function tests (Serum levels of TSH, FT3 and FT4).

In addition, the researcher tried to determine whether we can consider these changes in serum irisin and serum CK levels in thyroid dysfunction as markers for diagnosis of hypo-and hyperthyroi-dism in rats.

This study observed a significant decrease in serum irisin levels in hypothyroid rats and a significant increase of its levels in hyperthyroid rats. Also a

negative correlation between serum irisin levels and serum TSH levels and a positive correlation between irisin and both FT3, FT4 serum levels were recorded.

These findings are consistent with the study of **Ruchala et al. (2014**), who observed that serum Irisin levels were lower in hypothyroid than hyperthyroid patients, and demonstrated a negative correlation between irisin and TSH levels, as well as a positive correlation between irisin and FT4 levels.

However, **Samy et al. (2015)** reported that in both hypo-and hyperthyroid rats there were elevation of serum irisin levels in response to myopathy and oxidative damage respectively observed in both conditions and they found no significant correlation between irisin and TSH serum levels.

Also, **Stengel et al. (2013)** found no associations between levels of irisin, TSH and thyroid hormones in euthyroid individuals. Their study was on obese and anorexia nervosa patients with no impairment of thyroid functions.

On the other hand, **Zybek-Kocik et al. (2016)** noticed that serum irisin levels in over hypothyroid patients seem to be changed with the duration of hypothyroidism suggesting that there is a significant decrease in serum irisin levels in long-lasting hypothyroidism, while short-term does not change irisin concentrations. They interpreted their findings according to **Scott et al. (2002)** as in case of long term hypothyroidism there is severe prolonged myopathy that might impair the function of muscle tissue as a hormone secreting organ leading to gradual decrease in serum irisin levels.

This study also recorded a significant increase in serum CK levels in hypothyroid rats as well as a significant decrease in its levels in hyperthyroid rats. Also, there was a positive correlation between serum CK and serum TSH levels as well as a negative correlation between serum CK levels and irisin, FT3 and FT4 levels. These data were in agreement with **Ruchala et al. (2014)**, who found that CK levels were negatively correlated with serum irisin, FT3 and FT4 concentrations. Also, **Tejomani et al. (2013)** detected a rise in total CK activity in both subclinical and overt cases of hypothyroidism, and found that CK activity is a negatively correlated with T3 and positively correlated with TSH.

McGrowder et al. (2011) demonstrated elevated serum CK activity in hypothyroidism and decreased in hyperthyroidism, and recorded a positive correlation between CK and TSH as well as a negative correlation between CK and FT4. They interpreted their results according to the thyrometabolic state. In hypothyroidism there is a reduction in glycolysis and oxidative phosphorylation resulting in a drop in ATP concentrations beyond a critical level that increases sarcolemmal membranes permeability to CK leading to its leakage from the cell **(Robinson et al., 1974)**. In hyper metabolic state, there is an increased in enzyme degradation that may contribute to low CK activity, or the hyper metabolic state makes sarcolemmal membrane less permeable than normal to the efflux of CK **(Doran, 1978)**.

Moreover, **Panag et al. (2012)** concluded that measurement of CK can be considered a good marker for diagnosis of

thyroid function disorders. It is significantly increased in hypothyroid and significantly decreased in hyperthyroid patients. They also reported a negative correlation between CK and FT3 possibly mediated at the level of gene expression as very high levels of FT3 have been documented to inhibit CK synthesis. They described their findings according to the direct role of T3 at the regulation of gene expression in stimulating or inhibiting the synthesis of different proteins by increasing or decreasing transcription **(Liu and Brent, 2005)**. On the other hand, it has been reported by **Samy et al. (2015)** that CK significantly elevated in both hypo-and hyperthyroid rats and these coincides with an increase in serum irisin levels.

Anastasilakis et al. (2014) observed a day-night rhythm for both serum irisin and CK levels. They observed that circulating irisin levels lower in the early morning at 6: AM, and reaches its peak levels at 9:PM. Serum CK shows a pattern completely different from that of irisin with progressive decrease in its levels from 9:AM to 3:AM, and these patterns of day-night rhythm for both irisin and CK do not support the hypothesis that irisin leaks from muscle cells in response to muscle damage.

Variations in results between this study and others may be related to the thyrometabolic state, the degree of muscle damage, the duration and the severity of the disease, and types of kits, the time of taking the samples.

CONCLUSIONS

Serum irisin level decreased and serum CK level increased in hypothyroid rats, and the reverse occurred in hyperthyroid rats. At the same time, serum TSH level negatively correlated with serum irisin level, and positively correlated with serum CK level.

Also, both FT3 and FT4 levels positively correlated with serum irisin level and negatively correlated with serum CK level. In addition, a negative correlation between serum irisin and CK is reported. This may be related to variations in the thyrometabolic state, or the ability of different levels of FT3 to stimulate or inhibit synthesis of different proteins by increasing or decreasing transcription, or both. So, serum irisin and CK levels can be considered as markers for diagnosis of hypo or hyperthyroidism in rats.

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تقييم مستوى الايريزين والكيرياتين كينيز فى الدم للجرذان ذات الإرتفاع والنقصان فى وظائف الغدة الدرقية

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خلفية البحث : يعد خلل وظائف الغدة الدرقية أحد الامراض الناتجة عن اضطرابات التمثيل الغذائى، والتى لا يعتمد فى تشخيصها على قياس مستوى هورمونات الغدة فقط . وهناك دلالات أخرى مثل قياس مستوى الايريزين والكيرياتين كينيز فى الدم والتى تظهر العلاقة بينهما وبين الإرتفاع والنقصان فى وظائف الغدة الدرقية.

الهدف من البحث : أجريت الدراسة لتقييم العلاقة بين مستوى الايريزين والكيرياتين كينيز فى الدم وخلل وظائف الغدة الدرقية فى ذكور الجرذان البيضاء .

مواد وطرق البحث: شملت الدراسة ثلاثين من ذكور الجرذان البيضاء وتم تقسيمهم الى ثلاث مجموعات متساوية : المجموعة الاولى ذات وظائف غدة درقية طبيعية ، والمجموعة الثانية ذات وظائف غدة درقية منخفضة ، والمجموعة الثالثة ذات وظائف غدة درقية مرتفعة . وقد تم قياس معامل كتلة الجسم للفئران فى نهاية البحث وتم قياس الهورمونات المختلفة لوظائف الغدة الدرقية بالإضافة إلى الإنسولين والسكر والايريزين والكرياتين كينيز بالدم .

النتائج: أظهرت النتائج علاقة سلبية بين الايريزين وهورمون تنشيط الغدة الدرقية فى مجموعتي الجرذان ذات الإرتفاع والإنخفاض فى وظائف الغدة الدرقية ، وكذلك أظهرت النتائج علاقة إيجابية بين الايريزين وهورمونات الغدة الدرقية بنفس المجموعتين . كما أظهرت النتائج علاقة إيجابية بين الكرياتين كينيز وهورمون تنشيط الغدة الدرقية ، وعلاقة سلبية مع هورمونات الغدة الدرقية بنفس المجموعتين .

الإستنتاج: مستوى الايريزين بالدم قل فى حالة إنخفاض وظائف الغدة الدرقية ، وإزداد فى حالة إرتفاعها . من ناحية أخرى، فإن الكيرياتين كينيز قد إزداد فى حالة إنخفاض وظائف الغدة الدرقية وقل فى حالة إنخفاضها . لذا، يعتبر الايريزين والكيرياتين كينيز من المؤشرات الدالة على تشخيص إرتفاع وإنخفاض وظائف الغدة الدرقية فى الجرذان .