Al-Azhar Med. J. *Vol. 46(1), January, 2017, 211-222*
DOI: 10.12816/0035549

A STUDY ON SERUM LEVEL OF NESFATIN-1 IN EXPERIMENTALY- INDUCED THYROID DISORDER IN ADULT MALE ALBINO RATS

By

Mohammed Abd El-Raouf El-Ghannam, Abeer Albiomy Khalefa, Ebtesam Mohammed Ibrahim and Nihal Ibrahim Hendy

Department of Physiology, Faculty of Medicine, Zagazig University

ABSTRACT

Background: Nesfatin-1, a polypeptide encoded in the N-terminal region of the protein precursor Nucleobindin2 (NUCB2), functions in the regulation of fat storage and hunger. Nesfatin-1 co-localizes with thyrotropin-releasing hormone (TRH) and has a role in affecting the membrane potential of TRH neurons in the posteroventral nucleus (PVN). Data about nesfatin-1 levels in thyroid dysfunction is limited and controversial.

Objective: This current study aimed to evaluate serum nesfatin-1 levels in the euthyroid, hypothyroid, and hyperthyroid rats.

Materials and methods: Forty two adult male albino western mature rats were divided into three equal main groups: **Group I** (Euthyroid) was used as control group, **Group II** (Hypothyroid) were treated with propylthiouracil for 4 weeks, and **Group III** (Hyperthyroid) were treated with eltroxin for 4 weeks. In all groups, serum glucose, insulin, nesfatin-1, T3, T4, TSH and lipid profile were assayed.

Results: In hyperthyroid group compared to control group**,** there were significant rise in serum levels of nesfatin-1, T3, T4, insulin, glucose, HDL and level of HOMA-IR and a significant decrease in serum level of TSH l. However, there was a non-significant change in serum level of nesfatin-1 in hypothyroid group compared to control group. Furthermore, there were significant elevations in serum level of TSH, TC, TG and LDL and significant decreases in serum level of T3, T4 and HDL in hypothyroid group. There was a significant positive correlation between serum nesfatin-1 levels with T3, T4, serum levels of insulin, glucose, HOMA IR and HDL and significant negative correlations between serum nesfatin-1 levels with serum TSH, LDL levels, food intake and BMI in hyperthyroid group. However, there were significant positive correlations between serum nesfatin-1 level with T3, and HDL, and a significant negative correlation between serum nesfatin-1 level with food intake in hyporthyroid group.

Conclusion: Hyperthyroid state was accompanied by increased nesfatin-1 level, while hypothyroid state did not influence the nesfatin-1 level.

Key words: Nesfatin-1, Thyroid disorder, Male albino rats.

INTRODUCTION

Nesfatin-1 polypeptide is encoded in the N-terminal region of the protein precursor Nucleobindin2 (NUCB2). It is a neuro-peptide created in mammalian hypothalamus and shares in the regulation of fat storage and hunger **(Oh-I et al., 2006)** .

Nesfatin-1 mRNA expression levels were 10-folds higher in gastric mucosa in comparison to the brain**,** suggesting the stomach being the major source of circulating nesfatin-1 **(Stengel et al.,**

2009).http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0071513 - pone.0071513-Stengel2

Studies has stated that nesfatin-1 crosses the brain blood barrier (BBB) through a non-saturable mechanism, giving the impression that nesfatin-1, released from the stomach, could be acting centrally **(Pan et al., 2007 and Price et al., 2007).**

Nesfatin-1 inhibits food intake and enhances glucose-stimulated insulin secretion in pancreatic beta-cells of mouse and rat **(Shimizu et al., 2009, Su et al., 2010, Nakata et al., 2011 and Li et al., 2013).**

In **2012**, **Yamawaki et al.** revealed that nesfatin-1 directly inhibits peripheral arterial wall smooth muscle relation via impairing the cGMP expression.

Thyroid hormones are also critical for maintenance of total energy consumption and body composition as well as their roles in normal development, growth and reproduction **(Aydogan and Sahin, 2013)**.

Moreover, a positive correlation between serum thyroid stimulating hormone (TSH) levels and body mass index (BMI) suggests that the dysfunction of thyroid gland is associated with weight alterations **(Sahin et al., 2014).** Hyper- and hypothyroidism are also associated with insulin resistance **(Lambadiari et al., 2011).**

Furthermore, thyroid disorders are accompanied by marked variations in the lipid profile which be due to the regulatory effect of THS on the activity of some essential enzymes of lipoprotein metabolism **(Stengel et al., 2009)**. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0071513 - pone.0071513-Stengel2

Nesfatin-1 co-localizes with thyrotropin-releasing hormone (TRH) and has a role in affecting the membrane potential of TRH neurons in the posteroventral nucleus (PVN) known to be strongly related to the regulation of thyroid function **(Price et al., 2008)**.

Interestingly, **Sawicka et al**. **(2010)** stated that the disturbed thyroid hormones levels are associated with the change of ghrelin production, while ghrelin was proved to be co-expressed with nesfatin-1 in gastric X/A-like endocrine cells.

Data about nesfatin-1 levels in thyroid dysfunction is limited and controversial. In hyperthyroidism, some reports showed that circulating nesfatin-1 levels were suppressed **(Sawicka and Bossowski, 2013),** while others detected that serum nesfatin-1 level was increased **(Tohma et al., 2015)**. However, others detected that serum nesfatin-1 level was not changed **(Gungunes et al., 2014)**.

In hypothyroidism, some investigators showed that serum nesfatin-1 levels decreased (**Sawicka and Bossowski, 2013)** or normal **(Sahin et al., 2014)**.

This study was designed to assess serum nesfatin-1 levels in the euthyroid, hypothyroid, and hyperthyroid rats in the trial to clarify the possible relationship between thyroid hormones, body weight changes, lipid profile, serum insulin, blood glucose levels, and the serum nesfatin-1 levels.

MATERIAL AND METHODS

Animals:

Forty two healthy adult male albino rats of a local strain weighing 180-200 grams per rat were used. They were provided by the Laboratory Animals Farm Unit, Faculty of Veterinary Medicine Zagazig University. The rats were kept in cages (40cmx28cmx18cm-six rats per cage) in the animal house of Faculty of Medicine Zagazig University. The rats were kept on mixed commercial rat laboratory chow. All animals had free water access. Rats were kept at room temperature, and were maintained on natural light/dark cycle **(Morovat and Dauncy, 1998)**.

The rats were allowed to adapt to the laboratory conditions for three weeks prior to starting the experimental regimen **(Canaris et al., 2000)**. These rats were divided into three equal groups:

- **Group I (Euthyroid):** All animals had free access to plain water for 4 weeks.
- **Group II (Hypothyroid):** Rats were treated with propylthiouracil administration in a dose of 50 mg/dl (0.05%) in drinking water for 4 weeks.
- **Group III (Hyperthyroid):** Rats were treated with eltroxin administration (T4), a dose of in 600 µg/dl (6×10^{-4} %) in the drinking water for 4 weeks.

Measurement of food intake: Equal amounts of food (30 g/day/rat) were provided to every rat in a separate compartment in the cage and the amount consumed by each rat was assessed **(Reinehr, 2010)**.

Estimation of BMI: BMI was calculated using the equation: Body weight (g) /lenght^2 (cm^2) = BMI (gm/cm^2) **(Saldanha et al., 2012).** Incidence of hyper- and hypothyroidism was confirmed by measurement of total T3, T4 and TSH.

Blood sampling: Blood samples were taken from retro orbital vein under ether anesthesia between 9-11 A.M. with animals overnight fasting. Clean plastic centrifuge tubes were used to collect the blood. Blood was then allowed to clot. Centrifugation at 3000 rpm for 15 minutes was done to separate serum of blood. The supernatant serum was stored frozen at -20 ?C until assayed for:

1. Serum glucose by enzymatic colorimetric method using Glucose (GOD-PAP) - liquizyme kits (Biotechnology, Egypt) according to **Gungunes et al. (2014)**.
2. Insulin by Enzyme Amplified Sensitivity Immunoassay Kits (BioSource Europe S.A., Belgium) according to **Starr et al. (1978)**.
3. Nesfatin-1 by rat enzyme immunoassay kits (Sun Red Biotecnology, Shanghai, Postcode: 201908) according to **Oh-I et al. (2006).**
4. T3, T4, TSH and lipid profile using enzyme linked immuo sorbant assay (ELISA) kits (M.B.S /Medical Biological Service, Milano- Italy).

Statistical analysis: Data were presented as mean ± SDM. Post-Hoc test was used with One way ANOVA test to determine statistical significance. P values less than 0.05 were considerable significant. Spearman's rank correlation was used to analyze the correlations between nesfatin-1 and other parameters. SPSS version 18 program for Windows (SPSS Inc. Chicago, IL, USA) was used for statistical analysis**.**

RESULTS

Table (1): Comparison between the studied groups as regard all measured parameters (Mean±SD).

Groups / Variables	Euthyroid Group I N=(14)	Hypothyroid Group II N=(14)	Hyperthyroid Group III N=(14)
Nesfatin-1 (ng/ml)	7.63±0.93	7.66±0.77	14.60±2.11[(a), (b)]
T3 (ng/ml)	1.56±0.25	0.73±0.21[(a)]	2.64±0.32[(a), (b)]
T4 (µg/ml)	5.29±1.40	0.78±0.22[(a)]	13.49±2.31[(a), (b)]
TSH (µIU/ml)	0.005±0.0003	0.009±0.0007[(a)]	0.003±0.0001[(a), (b)]
Glucose (mg/dl)	89.35±1.49	13.44±2.24	29.64±2.11[(a), (b)]
Insulin (µIU/ml)	11.98±1.45	13.44±2.24	29.64±2.11[(a), (b)]
HOMA-IR	2.645±0.36	3.01±6.52	9.77±0.81[(a), (b)]
TC (mg/dl)	93.29±10.53	237.79±30.03[(a)]	0.79±7.79 [(b)]
TG (mg/dl)	67.57±11.08	85.50±17.02[(a)]	58.60±8.2 [(b)]
HDL (mg/dl)	40.89±5.82	28.21±4.61[(a)]	46.35±9.11[(a), (b)]
LDL (mg/dl)	38.89±11.62	186.29±28.94[(a)]	21.72±9.54[(a), (b)]
BMI (gm/cm^2)	0.62±0.05	0.74±0.075[(a)]	0.55±0.035[(a), (b)]
Food intake (gm/kg BW/day)	72.36±4.41	64.50±4.18[(a)]	91.50±4.18[(a), (b)]

(a) P>0.05 versus group I; (b) P>0.05 versus group II.

Table (2): Correlation between all measured parameters and nesfatin-1 serum level.

Nesfatin-1 / Variables	Euthyroid Group I	Hypothyroid Group II	Hyperthyroid Group III
T3 (ng/ml)	0.98*	0.74*	0.93*
T4 (µg/ml)	0.98*	0.42	0.61*
TSH (µIU/ml)	-0.80*	-0.53	-0.56*
Glucose (mg/dl)	0.96*	0.459	0.98*
Insulin (µIU/ml)	0.95*	0.46	0.97*
HOMA-IR	0.95*	0.497	0.98*
TC (mg/dl)	0.023	0.024	0.41
TG (mg/dl)	0.30	0.29	-0.17
HDL (mg/dl)	0.79*	0.96*	0.98*
LDL (mg/dl)	-0.48	-0.15	-0.57*
BMI (gm/cm^2)	-0.22	-0.05	-0.57*
Food intake (gm/kg BW/day)	-0.65*	-0.58*	-0.98*

(*) Significant (P<0.05).

There was a significant increase in nesfatin-1 level in hyperthyroid group and a non significant change in hypothyroid group compared to control group. Also, there was a significant elevation in serum level of T3, T4, insulin, glucose, HDL, food intake and level of HOMA-IR, a significant reduction in serum level of TSH, LDL and BMI and a non-significant change in serum level of TC and TG in hyperthyroid group compared to control group. On the other hand there was a significant increase in serum level of TSH, TC, TG, LDL and BMI. Also, there was a significant decrease in serum level of T3, T4, HDL and food intake and non significant change in serum level of insulin, glucose, and level of HOMA-IR In hypothyroid group compared to control group (Table 1).

Significant positive correlations occured between serum nesfatin-1 levels with T3, T4, serum level of insulin, glucose, HOMA IR and HDL, and significant negative correlations between serum nesfatin-1 levels with serum TSH, LDL levels, food intake and BMI in hyperthyroid group. However, there was a significant positive correlation between serum nesfatin-1 level with T3, and HDL, and significant negative correlation between serum nesfatin-1 levels with food intake in hyporthyroid group, while there was no correlation between serum nesfatin-1 levels with other parameters TC and TG in all groups (Table 2).

DISCUSSION

Nesfatin-1 has many peripheral sites of production as in alpha and beta cells of islet of Langerhans, liver, subcutaneous, visceral fat tissues and brown adipose cells **(Gonzalez et al., 2011, Osaki et al., 2012, Zhang et al., 2012, and Ayada et al., 2015),** and skeletal muscle **(Kim et al., 2014).**

This study was designed to investigate the effect of thyroid gland state (eu-, hypo- and hyperthyroid) on serum nesfatin-1 levels.

In the present research, hyperthyroid model showed an increase in T3, T4, food intake and serum nesfatin-1 levels accompanied by a decrease in TSH and BMI when compared with control group.

However, in hypothyroidism, there was a significant decrease in T3, T4 and food intake with a significant elevation in TSH and BMI, while a non-significant change in serum nesfatin-1 level in the same group was detected when compared with control group.

These results were in agreement with a human study on hyperthyroid patients in comparison with healthy controls **(Tohma et al., 2015)**, and the results of **Sahin et al. (2014)** who stated that nesfatin-1 level had no significant change in patients with hypothyroidism when compared with same age and BMI matched healthy control group.

In the present research, a significant positive correlation were detected in all groups between nesfatin-1 and T3, and also significant positive correlation were detected in both eu- and hyperthyroid groups between nesfatin-1 and T4, and significant negative correlation with TSH in both eu- and hyperthyroid groups, and that was in line with a human study on patients with overt hyperthyroidism in comparison with healthy controls **(Gungunes et al., 2014 and Tohma et**

al., 2015) and on patients with T2DM **(Liu et al., 2014)**.

In the present study, the hyperthyroid group showed an elevation in the food intake and appetite, while BMI reduced. Appetite likely rose due to the action of thyroid hormones on the hypothalamic nuclei. Such nuclei were likely accountable for the rise of energy intake in hyperthyroid patients **(Feldt-Rasmussen, 2007 and Reinehr, 2010).**

However, the factors and mechanisms concerned with the increase in appetite during hyperthyroidism are not yet clarified. It has been suggested that T3 increases the formation of Aguti related peptide (AgRP) and neuro peptide Y (NPY) through acting on the Arcuat nucleus (ARC) (the center of food intake) via the ‘‘mammalian target of rapamycin’’ (mTOR) and uncoupling protein 2 (UCP2) **(Lo´pez et al., 2013).**

In addition, **Herwig et al. (2014)** found, in a rodent model, that T3 may play a direct role on AgRP mRNA expression in the ARC and nesfatin-1 acts as anorexogenic by decreasing the formation of AgRP and NPY via acting on the ARC.

Nesfatin-1 has been found in the mid portion of gastric glands localized with the orexigenic hormone ghrelin **(Stengel et al., 2009)**,which increase appetite and fat mass by triggering receptors in the ARC that include the orexigenic NPY neurons **(Herwig et al., 2014).**

So, the cause of increase nesfatin-1 level in hyperthyroid group may be to compensate marked increase of food intake and appetite. Moreover, there is a hypothesis that the increase of nesfatin-1 is to compensate the increase in food intake, and this is supported by negative correlation between nesfatin-1 and food intake in all groups. However, food intake cannot be considered as the main regulator of nesfatin-1 as its level not significantly changed in hypothyroid group in comparison with the control group in spite of decrease in food intake.

Statistically, nesfatin-1 level significantly increased in hyperthyroid group, but there was a non-significant change in nesfatin-1 level in hypothyroid group in spite of marked decrease of T3 and T4 levels, and marked increase of TSH level. These results proposed that changes in nesfatin-1 level were not directly due to changes of TSH levels.

In the present work, BMI was proved lower in the hyperthyroid group in comparison to the euthyroid group. These results were proved previously by **Saldanha et al. (2012)** who studied the changes in BMI and total body composition after radio-iodine treatment for thyrotoxicosis**,** as well as another study on clinical and subclinical hypothyroid patients **(Mercer and Barrett, 2014).**

In the present study, there was a significant negative correlation between nesfatin-1 and BMI in hyperthyroid group which was supported by **Tsuchiya et al. (2010)**.

Because nesfatin-1 increased BMR which lead to decrease BMI. Therefore, the increase of nesfatin-1 level in the hyperthyroid group may be responsible for decrease BMI, but the levels of nesfatin-1 in hyporthyroid group did not change in spite of increase BMI, and non significant correlation was present between nesfatin-1 and BMI in hypo-

thyroid group. So, changes in BMI alone cannot explain the changes in nesfatin-1 level.

In the current research, there was a significant elevation in TC,TG and LDL, and significant reduction in HDL in hypothyroid in comparison to the control group, while there was a significant reduction in TC,TG and LDL, and significant elevation in HDL in hyperthyroid in comparison to control group. These changes in lipid profile with thyroid dysfunction were previously proved **(Tan et al., 2011 and Denize et al., 2012).**

Also, in this study, there was a significant positive correlation between nesfatin-1 and HDL in all groups. However, there was a significant negative correlation between nesfatin-1 and LDL in hyperthyroid group. Also, there was a non-significant correlation between nesfatin-1 with TG and TC levels in all groups

These results can be supported by a study on obese subjects which found a non-significant correlation between nesfatin-1 with TG and TC. However, it also revealed a non-correlation between nesfatin-1 with HDL and LDL **(Abaci et al., 2013**).

A research on metabolic effects of nesfatin-1 in rats proved that models given nesfatin-1 consumed less food, utilized more of their stored fat, and became more active **(Price et al., 2008)**. Additionally, nesfatin-1 was concerned with feeling of satiety and affected lipid amounts by causing a decrease in subcutaneous and mesenteric fat after 24 h of fasting **(Oh-I et al., 2006**).

In spite of marked disturbance of lipid profile which occurred in hypothyroid group, there was no significant changes in serum nesfatin-1 level. So, changes in lipid profile with thyroid dysfunction cannot be the only explanation of the changed occurred in nesfatin-1 level.

In addition, our findings stated that there was a significant elevation in glucose, insulin levels and insulin resistance in hyperthyroid group. On the other hand, there was a non-significant increase in the previous parameter in hypothyroid group in comparison to control group.

These findings were in line with other studies which stated that, during hyperthyroidism, insulin half-life decreased most probably secondary to an elevated rate of catabolism and an improved release of biologically inactive insulin precursors **(Dimitriadis et al., 2006 and Mirella et al., 2011).**

Another mechanism clarifying the relation between hyperthyroidism and hyperglycemia produces an elevation in the hepatocyte plasma membrane levels of GLUT2 which is the key glucose transporter in the liver. Thus, the elevated levels of GLUT-2 share in the elevated hepatic glucose output and abnormal glucose metabolism **(Potenza et al., 2009).**

Moreover, a significant positive correlation was found between level of nesfatin-1 with glucose, insulin and HOMA IR levels in hyperthyroid group. That was in agreement with a study on obese human was done by **Tan et al. (2011)** and **Zhang et al. (2012)** where they found a significant positive correlation between level of nesfatin-1

with glucose, insulin and HOMA IR levels.

Nesfatin-1 has a direct glucose-dependent insulino-tropic action on β-cells of the pancreatic islets cell **(Su et al., 2010 and Gonzalez et al., 2011)**.

Insulin activates the expression of peroxisome proliferator-activated receptor-gamma (PPAR-gamma), and also PPAR-gamma agonists induce the activation of NUCB2 **(Oh- I et al., 2006)**.

Nesfatin-1 production significantly increased by insulin and dexamethasone as well as IL-6 and TNF-α **(Ramanjaneya et al., 2010)**.

Nesfatin-1 elevates the glucose-stimulated insulin production from pancreatic beta cells, and also acts on glucose metabolism via a direct peripheral mechanism to elevate insulin secretion and insulin sensitivity in the skeletal muscle, adipose tissue and liver **(Li et al., 2013).**

Plasma nesfatin-1 concentrations increased in patients with impaired glucose tolerance or new-onset T2DM **(Zhang et al., 2012)**.

In contrast, studies by **Abaci et al. (2013**) and **Sahin et al. (2014)** showed non-significant correlations between level of nesfatin-1 with glucose, insulin and HOMA IR levels.

Moreover, nesfatin-1 level significantly reduced in patients with newly diagnosed T2DM **(Li et al., 2013 and Liu et al., 2014)**. Species differences and the cause of T2DM may be a cause of this difference between these studies.

Therefore, increase level of nesfatin-1 in hyperthyroid group which suffered from sever insulin resistance was to improve disturbance in glucose metabolism, insulin and to compensate increase in insulin resistance.

In the current research, there was non-significant changes in glucose metabolism, insulin and insulin resistance in hypothyroid group in comparison to control group, and also level of nesfatin-1 did not significantly change in hypothyroid group compared to control group and that assure the explanation that increase level of nesfatin-1 in hyperthyroid group was to improve disturbance in glucose metabolism, and to compensate marked increase in insulin resistance.

CONCLUSION

Hyperthyroid state was accompanied by increased nesfatin-1 level, while hypothyroid state and not influence the nefatin-1 level. In hyperthyroid state, nesfatin-1 levels seemed to be related to serum insulin, blood glucose and insulin resistance, and not to serum T3, T4, food intake, BMI and lipid profile. Glucose metabolic parameter was the main regulator factor for circulating nesfatin-1 level in hyperthyroid state.

REFERENCES

1. **Abaci A, Catli G, Anik A, Kume T and Bober E (2013):** The relation of serum. Nesfatin-1 level with metabolic and clinical parameters in obese and healthy children. Pediatric Diabetes, 14: 189–195.

2. **Ayada C, Toru U and Korkut Y (2015):** Nesfatin-1 and its effects on different system. Hippokratia, 19(1):4-10.

3. **Aydogan BI and Sahin M (2013):** Adipocytokines in Thyroid Dysfunction J Clin Endocrinol Metab., 91(12):4930–4937.

4. **Canaris GJ, Manowitz NR, Mayor G and Ridgway C (2000):** The Colorado thyroid disease prevalence study. Arch Intern Med.,160: 526-534.

5. **Deniz R, Gurates B, Suleyman Aydin S, Celik H, Sahin I, Baykus Y, Catak Z, Aksoy A, Citil C and Sami Gungor S (2012):** Nesfatin-1 and other hormone alterations in polycystic ovary syndrome. Endocrine, 42:694–699

6. **Dimitriadis G, Mitrou P, Lambadiari V, Maratou E and Raptis SA (2006)**: Insulin action in adipose tissue and muscle in hypothyroidism, J Clin Endocrinol Metab., 91(12):4930–4937.

7. **Feldt-Rasmussen U (2007):** Thyroid and leptin. Thyroid, 17(5):413–419.

8. **Gonzalez R, Perry RL, Gao X, Gaidhu MP, Tsushima RG, Ceddia RB and Unniappan S (2011):** Nutrient responsive nesfatin-1 regulates energy balance and induces glucose-stimulated insulin secretion in rats. Endocrinology ,152(10): 3628–3637.

9. **Gungunes A, Ozbek M, Ginis Z, Sahin M, Demirci T, Cakir ,Ozkaya E, Karbek B and Sayki Arslan M (2014):** Serum nesfatin-1 levels in overt and subclinical hyperthyroidism. Minerva Endocrinol., 39:209–214**.**

10. **Herwig A, Campbell G, Mayer CD, Boelen A, Anderson RA, Ross AW, Hewson AK and Dickson SL (2014):** "Systemic administration of ghrelin induces Fos and Egr-1 proteins in the hypothalamic arcuate nucleus of fasted and fed rats". J .Neuroendocrinol., 12 (11): 1047–1049.

11. **Kim J, Chung Y, Kim H, Im E, Lec H and Yang H (2014):** The tissue distribution of Nesfatin-1/ NUCB2in mouce. Dev. Reprod., 18(4):301-309.

12. **Lambadiari V, Mitrou P, Maratou E, Raptis AE, Tountas N, Raptis SA and Dimitriadis G (2011):** Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes. Endocrine, 39(1):28-32**.**

13. **Li Z, Gao L, Tang H, Yin Y, Xiang X, Li Y, Zhao J, Mulholland M and Zhang W (2013):** Peripheral effects of nesfatin-1 on glucosehomeostasis. Minerva Endocrinol., 18 (8):e71513-e71521.

14. **Liu E, Yang Q, Gao N, Liu F and Chen S (2014):** Decreased Plasma nesfatin-1 level is related to the thyroid dysfunction in patients with type 2 diabetes mellitus. Journal of Diabetes Research, 152(10): 3628–3637

15. **Lo´pez M, Alvarez CV, Nogueiras R and Die´guez C (2013):** Energy balance regulation by thyroid hormones at central level. Trends Mol Med., 19:418–427.

16. **Mercer JG and Barrett P (2014):** A thyroid hormone challenge in hypothyroid rats identifies T3 regulated genes in the hypothalamus and in models with altered energy balance and glucose homeostasis. Thyroid, 24:1575–1593.

17. **Mirella H, Mira S Z and Sami T A (2011):** Thyroid Disorders and Diabetes Mellitus. Journal of Thyroid Research, 39(1):28-32**.**

18. **Morovat M and Dauncey MJ (1998**): Effect of thyroid status on insulin- like growth factor-I, growth hormone and insuline are modified by food intake. European Journal of Endocinology, 138: 95-103.

19. **Nakata M, Manaka K, Yamamoto S, Mori M and Yada T (2011**): Nesfatin-1 enhances glucose-induced insulin secretion by promoting Ca(2+) influx through L-type channels in mouse islet beta-cells. Endocr J., 58: 305–313.

20. **Oh- I S, Shimizu H, Satoh T, Okada S, Adachi S, Inoue K, Eguchi H, Yamamoto M, Imaki T, Hashimoto K, Tsuchiya T, Monden T, Horiguchi K, Yamada M and Mori M (2006):** Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature, 443:709–712.

21. **Osaki A , Shimizu H, Ishizuka N, Suzuki Y, Mori M and Inoue S (2012):** Enhanced expression of nesfatin/nucleobindin-2 in white adipose tissue of ventromedial hypothalamuslesioned rats. Neurosci Lett., 11: 46–51.

22. **Pan W, Hsuchou H and Kastin AJ (2007):** Nesfatin-1 crosses the blood-brain barrier without saturation. Peptides, 28: 2223–222.

23. Potenza M, Via MA and Yanagisawa RT (2009): Excess thyroid hormone and carbohydrate metabolism. Endocr Pract., 15(3):254-262.

24. Price CJ, Samson WK and Ferguson AV (2008): Nesfatin-1 inhibits NPY neurons in the arcuate nucleus. Brain Res., 1230: 99–106.

25. Price CJ, Samson WK, Niehoff ML *and* Banks WA *(*2007*):* Permeability of the blood-brain barrier to anovel satiety molecule nesfatin-1. Peptides, 28*:* 2372–2381.

26. Ramanjaneya M, Chen J, Brown JE, Tripathi G, Hallschmid M, Patel S, Kern W, Hillhouse EW, Lehnert H, Tan BK and Randeva HS (2010): Identification of nesfatin-1 in human and murineadipose tissue: a novel depot-specific adipokine with increased levels in obesity. Endocrinology, 151(7):3169-3180.

27. Reinehr T (2010): Obesity and thyroid function. Molecular and Cellular Endocrinology, 316(2):165–171.

28. Sahin S B , Ayazb T, Cumhur Curec M, Sumerb F and Ilkkilicb K (2014): Association of nesfatin-1 levels with fasting and post load glucose levels in patients with hypothyroidism. J. Exp. Clin. Med., 31:217-220 .

29. Saldanha JF, Carrero JJ, Lobo JC ,Stockler-Pinto MB, Leal VO, Calixto A, Geloneze B and Mafra D (2012): The newly identified anorexigenic adipokine nesfatin-1 inhemodialysis patients: Are there associations with food intake, body composition and inflammation? J.R egul Pep., 173: 82–85.

30. Sawicka B and Bossowski A (2013): Analysis of serum levels of nesfatin-1 in children and adolescents with autoimmune thyroid diseases. Pediatr Endocrinol Diabetes Metab., 19: 5–10.

31. Sawicka B, Bossowski A, Szalecki M , Wysoka J and Koput A (2010): "Relationship between metabolic parameters and thyroid hormones and the level of gastric peptides in children with autoimmune thyroid diseases,". Journal of Pediatric Endocrinology and Metabolism, 23(4): 345–354.

32. Shimizu H, Oh-I S, Hashimoto K, Nakata M, Yamamoto S, Yoshida N, Eguchi H, Kato I, Inoue K, Satoh T, Okada S, Yamada M, Yada T and Mori M (2009): Peripheral administration of nesfatin-1 reduces food intake in mice: the leptin-independent mechanism. Endocrinology, 150: 662–671.

33. Starr JI, Mako ME, Juhn D and Rubenstein AH (1978): Measurement of serum pro-insulin–like material: cross reactivity of porcine and human proinsulin. J. Lab. Clin. Med., 91:691-692**.**

34. Stengel A, Goebel M, Yakubov I, Wang L, Witcher D, Coskun T, Taché Y, Sachs G and Lambrecht NW (2009): Identification and characterization of nesfatin-1 immunoreactivity in endocrine cell types of the rat gastric oxyntic mucosa. Endocrinology, 150(1):232–238.

35. Su Y, Zhang J, Tang Y, Bi F and Liu J-N (2010): The novel function of nesfatin-1: anti-hyperglycemia. Biochemical and Biophysical Research Communications, 391(1) : 1039–1042.

36. Tan BK, Hallschmid M, Kern W, Lehnert H and Randeva HS (2011): Decreased CSF /plasma ratio of the novel satiety molecule, nesfatin-1/NUCB-2, in obese humans: evidence of nesfatin-1/NUCB-2 resistance and implications for obesity treatment. J Clin Endocrinol Metab., 96: 669–673.

37. Tohma Y, Akturk M, Altinova A, Yassibas E, Ethem Turgay C, Gulbahar O, Arslan M, Sanlier N and Toruner F (2015): Circulating Levels of Orexin-A, Nesfatin-1, Agouti-Related Peptide, and Neuropeptide Y in Patients with Hyperthyroidism. Thyroid , 25: 662–671.

38. Tsuchiya T, Shimizu H, Yamada M, Osaki A, Oh-I S, Ariyama Y, Takahashi H, Okada S, Hashimoto K, Satoh T, Kojima M and Mori M (2010): Fasting concentrations of nesfatin-1 are negatively correlated with body mass index in non-obese males. Clinical Endocrinology, 73(4):484-490.

39. Yamawaki H, Takahashi M , Mukohda M, Morita T, Okada M and Hara Y (2012): A novel adipocytokine, nesfatin-1 modulates peripheral arterial contractility and blood pressure in rats. Biochemical and biophysical research communications, 418(4): 676-681.

40. Zhang Z, Li L, Yang M, Liu H, Boden G and Yang G (2012): Increased plasma levels of nesfatin-1 in patients with newly diagnosed type 2 DM. Exp Clin Endocrinal Diabetes, 120 (2): 91–95.

دراسة عن مستويات النسفاتين-١ في مصل دم ذكور الجرذان البيضاء البالغة المحدث بها خلل في وظائف الغدة الدرقية تجريبيا

محمد عبد الرؤوف الغنام، عبير البيومي خليفة، ابتسام محمد إبراهيم، نهال إبراهيم هندي

قسم الفسيولوجيا – كلية طب الزقازيق

خلفية البحث : إن هرمونات الغدة الدرقية وكذالك الاديبوسيتوكينات تؤثر وتتأثر بكتلة الجسم ومحتواه الدهني والشهية للطعام وتوليد الحرارة ومستوي الجلوكوز والدهون بالدم وكذلك مدي حساسية مستقبلات الإنسولين.

وجدير بالذكر ان النيسفاتين -١هو أحد الأديبوسيتوكينات الذي تم إكتشافه عام ٢٠٠٦في الجهاز العصبي المركزي (في بعض من نويات ما تحت المهاد المخي) .

وقد يكون للنيسفاتين- ١ علاقه بمستوي هرمونات الغدة الدرقية أو بالخلل الأيضي الناجم عن زيادة أو نقص وظائف الغدة الدرقية.

الهدف من البحث: إستكشاف ما إذا كان خلل وظائف الغدة الدرقية قد يؤثر علي مستويات النسفاتين -١ في مصل الدم وإذا ما كان له دور في الخلل الأيضي الناجم عن زيادة أو نقص نشاط الغدة الدرقية .

مواد و طرق البحث: تم اجراء هذه الدراسة على عدد ٤٢ من ذكور الجرذان البيضاء البالغة (نفس الفئة العمرية"١٦ اسبوع" ومتقاربة الوزن"١٨٠-٢٠٠ جرام" وتم تقسيمها إلى ٣ مجموعات متساوية:

١- جرذان سليمة (مجموعة ضابطة) .
٢- جرذان محدث بها زيادة في نشاط الغدة الدرقية دوائيا .
٣- جرذان محدث بها نقص في نشاط الغدة الدرقية دوائياً .

وفي نهاية العمل (بعد ٤ أسابيع) تم حساب كل من مؤشركتلة الجسم و معدل إستهلاك الغذاء، ثم تم تخدير الجرذان واخذ عينة الدم من تجويف الوريد المحي، وتم قياس مستوي :

١) النسفاتين-١ .
٢) الثيروكسين-٣ والثيروكسين- ٤ و الهرمون المحفز للغدة الدرقية .
٣) الجلوكوز و الإنسولين و معدل الممانعة للإ نسولين .
٤) الكوليستيرول و الكوليستيرول عالي الكثافة والكوليستيرول منخفض الكثافة وثلاثي الجلسريدات.

النتائج :

- حدثت زيادة ذات دلالة إحصائية في مستويات النسفاتين-١ في مصل الجرذان المصابة بزيادة في هرمونات الغدة الدرقية مقارنة بالمجموعة الضابطة، كما حدث نقص ليس له دلالة إحصائية في مستويات النسفاتين-١ في الجرذان المصابة بنقص في هرمونات الغده الدرقية مقارنة بالمجموعة الضابطة.
- وجود معامل إرتباط ايجابي ذو دلالة إحصائية بين مستويات النسفاتين-١ ومستويات هرمون ثلاثى أيودو الثيروكسين ومستويات الإنسولين و الجلوكوز و معدل الممانعة للإنسولين والكوليستيرول عالي الكثافة ومصحوبًا بمعامل إرتباط سلبي ذو دلالة إحصائية بين مستويات النسفاتين-١، والهرمون المنشط للغدة الدرقية، والكوليستيرول منخفض الكثافة، ومؤشركتلة الجسم، و معدل إستهلاك الغذاء في مصل الجرذان المصابة بزيادة في هرمونات الغدة الدرقية مقارنة بالمجموعة الضابطة.
- وجد معامل إرتباط إيجابي ذو دلالة إحصائية بين مستويات النسفاتين-١ ومستوي هرمون ثلاثى أيودو الثيروكسين والكوليستيرول العالي الكثافة، ومصحوبًا بمعامل إرتباط سلبي ذو دلالة إحصائية بين مستويات النسفاتين-١ والكوليستيرول منخفض الكثافة، و معدل إستهلاك الغذاء في مصل الجرذان المصابة بنقص في هرمونات الغدة الدرقية.

الاستنتاج:

- إفراز هرمونات الغدة الدرقية ليس لها دور مؤثر في تغيير مستويات النسفاتين-١ بمصل الدم .
- التغيرات في مستويات الإنسولين و الجلوكوز ومعدل الممانعة الناتجة عن الخلل في زيادة هرمونات الغدة الدرقية لها دور مؤثر في تغيير مستويات النسفاتين-١ بمصل الدم .