# Pattern of Serum Irisin Hormone in Patients with Thyroid Dysfunction

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**ABSTRACT:**

**BACKGROUND:**

The protein irisin is one of the most recent hormone-like adipo-myokine, which have an important role in controlling energy metabolism in humans. Both thyroid hormones & irisin have some similarities in regulation of body metabolism, such as thermogenesis & energy balance.

**OBJECTIVE:**

To assess the association & correlation between serum irisin & thyroid hormones in hypothyroid & hyperthyroid patients as compared to normal individuals.

**PATIENTS AND METHODS:**

This work is a cross-sectional case-control study, involving 150 participants (50 with primary hypothyroidism, 50 with primary hyperthyroidism, & 50 healthy controls). Withdrawal of serum samples were done to estimate irisin level, triiodothyronine(T3), tetraiodothyronine (T4), thyroid stimulating hormone(TSH), glucose, lipid profile, urea, & creatinine.

**RESULTS:**

In hypothyroid group the mean irisin concentration was higher than hyperthyroid & normal controls (P=0.05). A significant positive correlation between irisin & TSH levels was identified (r: 0.201, p = 0.014). The correlation of irisin with T3 was negative (r : -0.180, p = 0.027) while with T4 was highly negative (r : -0.212, p= 0.009).

**CONCLUSIONS:**

The mean serum level of irisin was higher in hypothyroid patients than healthy controls, while the hyperthyroid patients had the lowest levels. Serum irisin was correlated positively with TSH & negatively with T3 & T4.

**KEYWORDS:** Adipokines; Endocrine; Hypothyroidism; Hyperthyroidism

## INTRODUCTION:

Human homeostasis of energy is regulated mainly by lifestyle conditions, but genetic disposition is also contributing to energy expenditure. There is great advance in our knowledge about effect of fatty tissues on endocrine system & metabolism (1). For homeostasis adipose tissues play an important role as an active endocrine organ. In the last few years a bulk of signal mediating adipo-cytokines were found to have valuable effect in metabolism regulation in several organs (2–4).

On the other hand, thyroid axis hormones are vital for the regulation of body constitution & total energy utilization in addition to their roles in normal growth & reproduction (5).

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Imbalances in the regulation of thyroid gl& hormones are one of the major public health problems worldwide, affecting body metabolism & promote inflammation (6). Many reports explored complex relation between thyroid hormones & adipo-cytokines (4). White adipose tissues are known to secrete many hormones like, Leptin (7,8), Ghrelin (9), Nisfatin, & newly-discovered Irisin (10). Irisin is presumed as an antidiabetic & antiobesity by regulating glucose homeostasis & fat tissue metabolism via converting white to brown adipose tissue(BAT) (1,11). For this reason irisin has gained popularity as a research material in many centers (12).

To increase fat oxidation & thermogenesis irisin express the uncoupling protein 1 (UCP1) in the mitochondrial outer membrane (13).

Fibronectin type III domain containing 5 (*Fndc5)*, the m-RNA precursor of irisin, was shown in many other tissues including thyroid gland (14) & adipose tissues.

That is why, irisin classified in both adipo-kine (10) & myo-kine families (11).

There is paucity of knowledge about the relations of irisin with the thyroid disorders, although the relations of irisin with several other illnesses has been explored (15). Raised TSH stimulate receptors on the adipocytes that enhances adipo-genesis through pre-adipocyte differentiation (16). It has been shown that BAT of hyperthyroid patients have more muscle metabolism & glucose uptake, in comparison to normal subjects, while raised TSH had an opposite relation to the BAT (17). BAT production was associated with high TSH in hypothyroid patients in other report (18). The first pioneers who studied irisin in recently diagnosed thyroid patients & its relation to serum creatine kinase (a muscle injury marker) reported a lower serum irisin in hypothyroid patients than in hyperthyroid patients (19). Long lasting hypothyroid patients have less irisin than those with short duration (20). In contrary, workers on animal models reported no obvious association between serum Irisin & metabolic abnormalities in thyroid dysfunction (21). Whereas, others found the correlation between TSH & irisin to be negative, while the correlation between free-T4 (FT4) & irisin to be positive. Conversely, a positive correlation between Irisin level & TSH, but a negative correlation with the FT4 were identified in patients with Hashimoto´s thyroiditis (15). Surprisingly, one report suggested that proposed metabolic effects of Irisin are most likely independent from thyroid axis hormone (22). Due to these controversies, further studies on irisin relations needed to be explored in human, which were mostly attributable to a number of drawbacks or limitations in the assay methods.

## AIMS OF THE STUDY:

To assess the associations & correlations of irisin hormone with thyroid function status, in a predefined thyroid patient groups & compare it with a healthy control group, together with other variables such as age, gender, residence, co-morbidity & anthropometric parameters in both hypothyroidism & hyperthyroidism. We also attempt to assess the validity of serum irisin level as a predictor for diagnosis of thyroid dysfunction.

## METHODS & MATERIALS:

**Study design & subjects:** this cross-sectional case control study, involved 150 participants. The blood samples were collected according to the Ethical Committee at the College of Medicine approval (approval no.32, date 12/1/2016), together with an informed consent, which has been taken from the involved participants. The cohort recruitment was subdivided into, (a) 50 patients with primary hypothyroidism, (b) 50 patients with primary hyperthyroidism, (c) 50 euthyroid healthy control with absence of acute or chronic illness (i.e. people who visits the laboratory for regular checking with no history of thyroid diseases & have normal serum T3, T4 & TSH levels).

**Sample collection:** Five milliliter of venous blood was drawn from cubital vein of each individual using disposable syringes, collected in plain gel tubes & let to clot at room temp. for 20 min.. The serum was isolated by centrifugation at speed of 3000 rpm for 20 min., & then kept at -70$^{o}$C for future analysis.

**Measurement of body mass index (BMI):** Measurements of body weight & height were done for all individuals according to standard procedure for obese scale BMI (23).

**Measurement of waist circumference (WC):** A tape measure was put in a horizontal level around the belly at a level just above both iliac crests. The estimation had been done when the normal expiration ended (24).

**Inclusion & exclusion criteria:** Adult patients (18-65 year) with primary hypothyroidism or primary hyperthyroidism were enrolled. Individuals with Euthyroid state were selected as controls. Patients with diabetes (25), chronic renal failure (26), regular forceful exercise (27), pregnant women (28) & patients with any other critical illnesses (29), were excluded.

**Measurement of biochemical parameters*:*** Human serum irisin was assayed with enzyme-linked immune sorbent assay (ELISA) technique, based on biotin double antibody sandwich ELISA kit from (Shanghai Lisa Zak biotechnology). The thyroid hormones assay principle combined an enzyme immunoassay competition method (T3 & T4) & sandwich methods (TSH) with a final fluorescent detection.

The levels of glucose, lipid profile, urea, and creatinine were measured using Cobas c 311 automated analyzer systems (Roche Diagnostics).

**Statistical analysis:** Statistical Package for Social Sciences (SPSS IBM-version 21.0) was used for data analysis. The following statistical tests were used (as illustrated in the text, tables & figures): Kolmogorov Smirnov, Chi-square, Fishers exact, t-test, one-way ANOVA, & ROC curve & AUC test. In all the statistical analysis level of significance (p-value) set at $\leq 0.05$.

## RESULTS:

**Socio-Demographic Distribution:**

The mean age of the 150 recruited participants was 40.8 ±12.3 years. The female/male ratio was 3.7/1. The higher proportions of participants 58 (38.7%) were housewives & most of them 126 (84%) were living in urban areas (Table -1). There was no significant difference between the participants regarding their age, gender & residence (p>0.05). Interestingly, there was a significant association between hypothyroidism cases & occupation as housewives (p=0.002) (Table -1).

**Table 1: Socio-demographic characteristics of the study groups with respect to age, gender, occupation & residence.**

| | Hypothyroidism | | Hyperthyroidism | | Healthy Control | | $\chi^2$ | P value |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | | |
| **Age(years)** | | | | | | | 7.1* | 0.5 |
| <20 | 3 | 6.0 | 1 | 2.0 | 1 | 2.0 | | |
| 20-29 | 4 | 8.0 | 11 | 22.0 | 10 | 20.0 | | |
| 30-39 | 14 | 28.0 | 11 | 22.0 | 13 | 26.0 | | |
| 40-49 | 15 | 30.0 | 16 | 32.0 | 11 | 22.0 | | |
| ≥50 | 14 | 28.0 | 11 | 22.0 | 15 | 30.0 | | |
| **Gender** | | | | | | | 2.4 | 0.2 |
| Male | 7 | 14.0 | 12 | 24.0 | 13 | 26.0 | | |
| Female | 43 | 86.0 | 38 | 76.0 | 37 | 74.0 | | |
| **Occupation** | | | | | | | 15.0 | **0.002** |
| Housewife | 24 | 48.0 | 23 | 46.0 | 11 | 22.0 | | |
| Student | 5 | 10.0 | 8 | 16.0 | 3 | 6.0 | | |
| Public servant | 9 | 18.0 | 6 | 12.0 | 13 | 26.0 | | |
| Self-employed | 12 | 24.0 | 13 | 26.0 | 23 | 46.0 | | |
| **Residence** | | | | | | | 2.6 | 0.2 |
| Urban | 42 | 84.0 | 39 | 78.0 | 45 | 90.0 | | |
| Rural | 8 | 16.0 | 11 | 22.0 | 5 | 10.0 | | |

*(*) Fishers exact test, ($X^2$), Chi-square, & (P) Probability.*

**Thyroid Function & metabolic Status of the participants:**

The mean TSH level of all participants was 16.5 ± 31 µIU/mL (Table -2), where 33.33% of them had low TSH, 33.3% high TSH & 33% normal TSH values, as expected reflecting patient groups: hypothyroidism, hyperthyroidism, & healthy control groups, respectively. Whereas, the mean T3 & T4 level of all participants were 1.98 ± 1.3 nmol/L & 102.5 ± 57.5 nmol/L respectively.

For comparison, the estimated mean of TSH, T3, T4 values where analyzed in the healthy control, hypothyroid & hyperthyroid groups. The glycemic state & renal function of all the studied samples were normal. The mean random blood glucose (RBG), blood urea & serum creatinine were 101.9 ± 13.2 mg/dl, 32.9 ± 9 mg/dl & 2.68 ± 1.98 µg/ml respectively. The mean irisin level of all the study members was 2.68 ± 1.98 µg/ml (Table -2).

**Table 2: Thyroid hormones (TSH, T3 & T4), Random blood glucose (RBG), Urea, Creatinin & Irisin concentrations in serum of the participants**

| Parameters | No. | Mean±SD | Hypothyroid | Hyperthyroid | Healthy Control | P value |
|---|---|---|---|---|---|---|
| **Participants** | 150 | --- | 50 (33.3%) | 50 (33.3%) | 50 (33.3%) | |
| **TSH (µIU/L)** | 150 | 16.5±31 | 50 (>5.0) | 50 (<0.25) | 50 (0.25 – 5.0) | 0.000* |
| **T3 (nmol/L)** | 150 | 1.98±1.3 | 14 (<0.9) | 31 (>2.33) | 105 (0.9 –2.33) | 0.000* |
| **T4 (nmol/L)** | 150 | 102.5±57.5 | 39 (<60) | 50 (>120) | 61 (60 – 120) | 0.000* |
| **RBG (mg/dl)** | 150 | 101.9 ± 13.2 | 101.360 | 107.880 | 96.560 | 0.000* |
| **Urea (mg/dl)** | 150 | 32.9 ± 9 | 36.7 | 36.3 | 25.6 | 0.000* |
| **Creatinin(mg/dl)** | 150 | 0.8 ± 0.4 | 0.89 | 0.83 | 0.79 | 0.011* |
| **Irisin (µg/ml)** | 150 | **2.68 ± 1.98** | **3.2±2.4** | **2.2±1.1** | **2.5±1.9** | **0.050*** |

*(SD) Standard Deviation, (P) Probability, *ANOVA test.*

**BMI & Waist Circumference (WC) of Participants:**

Following BMI & WC measurements, the majority of study participants were selected to be free from any known co-morbidities, although 8.7% had hypertension & 1.3% had hyperlipidemia, but majority were in the healthy control group (Table -3). A high significance association was observed between obesity & hypothyroidism cases (p=0.005). Hypothyroid cases had very high significant correlation with increased waist circumference compared to other study groups (p<0.001) (Table -3).

**Table 3: Distribution of BMI, WC & co-morbidity of all participant groups hypothyroidism, hyperthyroidism & healthy controls**

| Variable | Hypothyroidism | Hyperthyroidism | Healthy Control | $\chi^2$ | P value |
|---|---|---|---|---|---|
| | No. (%) | No. (%) | No. (%) | | |
| **BMI** mean±SD (27.2±5.3 Kg/m$^2$) | | | | 14.7 | **0.005** |
| Normal (18.5-24.9) | 12 (24.0) | 27 (54.0) | 13 (26.0) | | |
| Overweight (25-29.9) | 20 (40.0) | 17 (34.0) | 21 (42.0) | | |
| Obese (30-39.9) | 18 (36.0) | 6 (12.0) | 16 (32.0) | | |
| **WC** mean±SD (94.1±12.7 cm) | | | | 18.2 | **<0.001** |
| Below mean | 12 (24.0) | 33 (66.0) | 20 (40.0) | | |
| Above mean | 38 (76.0) | 17 (34.0) | 30 (60.0) | | |
| **Co-morbidity** | | | | 16.1* | 0.003 |
| Negative | 46 (92.0) | 49 (98.0) | 40 (80.0) | | |
| Hyperlipidemia | 2 (4.0) | 0 | 0 | | |
| Hypertension | 2 (4.0) | 1 (2.0) | 10 (20.0) | | |

*(SD) Standard deviation, (*) Fishers exact test, ($X^2$) Chi-square, (P) Probability, (BMI) Body mass index, (WC)* Waist Circumference.

**Irisin & Thyroid Dysfunctions:**

The mean irisin level of all participants was 2.68±1.98 µg/ml. The higher irisin mean level was significantly associated with hypothyroidism, 3.2 ± 2.4 µg/ml (p=0.05), while lower irisin mean level was associated with hyperthyroid cases, 2.2±1.1 µg/ml. The irisin mean level in the control group was 2.5±1.9 µg/ml (Table -2 & Figure -1).

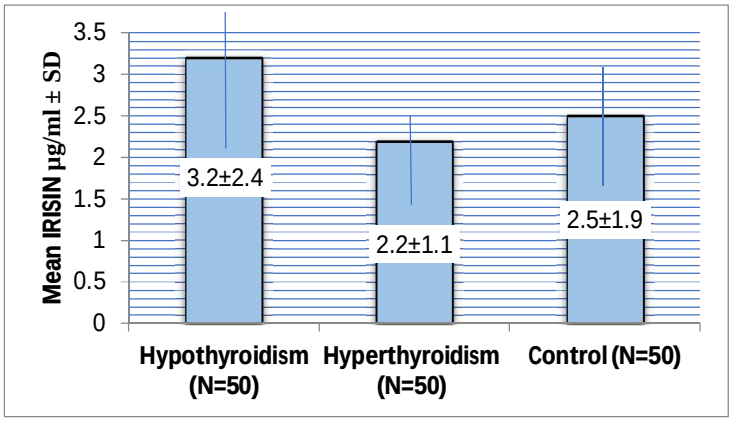


**Figure 1: Distribution of the irisin level for the study groups.**
*(SD) Standard Deviation, (N) Sample Number.*

There was a significant positive correlation between irisin & TSH levels (r:0.201*, p= 0.014) & negative correlation between irisin & T3 levels (r: -0.180*, p= 0.027), on other extreme the correlation between irisin & T4 was highly significant negative (r: -0.212**, p= 0.009) (Table -4).

**Table 4: Pearson correlation between irisin level & thyroid function tests (TSH, T3 & T4)**

| Groups | Irisin µg/ml | | | Comment |
|---|---|---|---|---|
| | Pearson corr. | P value | No. | |
| TSH | 0.201* | 0.014 | 150 | **Significant positive correlation** |
| T3 | -0.180* | 0.027 | 150 | **Significant negative correlation** |
| T4 | -0.212** | 0.009 | 150 | **Highly significant negative** |

*(P) Probability, (*) Significant correlation ≤ 0.05, (**) Highly significant correlation ≤ 0.01.*

**Irisin & Anthropometric Parameters:**

The mean irisin level was significantly higher among hypothyroid patients with higher WC (above the mean) (p=0.008) (Figure -2 & Table -5). We could not find significant differences in irisin levels related to WC among hyperthyroidism & controls (p>0.05) or BMI of all study participants (p>0.05) (Table -5).

**Table 5: The mean irisin according to *Waist circumference (WC) & Body mass index(BMI)* of study participants**

| Groups | Irisin (Mean±SD) µg/ml | | |
|---|---|---|---|
| | Hypothyroidism | Hyperthyroidism | Healthy Control |
| **WC cm** mean±SD (94.1±12.7) | | | |
| Above mean | 4.8±4.1 | 2.4±1.0 | 2.9±2.8 |
| Below mean | 2.6±1.4 | 1.9±0.7 | 2.3±0.4 |
| ***P value**** | **0.008** | 0.2 | 0.2 |
| **BMI kg/m2** | | | |
| Normal (18.5-24.9) Kg/m2 | 2.3±1.5 | 2.3±1.1 | 2.5±0.5 |
| Overweight (25-29.9) | 2.8±2.9 | 2.2±1.3 | 2.9±2.8 |
| Obese (30-39.9) | 3.6±2.5 | 2.8±1.9 | 2.1±0.7 |
| ***P value*** ** | 0.6 | 0.9 | 0.4 |

*(SD) Standard Deviation, (P) Probability, (*) t-test, (**) ANOVA.*

**Irisin in Prediction of Hypothyroidism:**

The cut off points & the corresponding validity tests values (sensitivity & specificity) for irisin in prediction of hypothyroidism are showed a value of 2.29 µg/ml with validity results: 52% sensitivity & 50% specificity (Figure -2).

Regarding screening uses, the irisin value of 2.01 µg/ml had sensitivity of 70% & specificity of 18%, while for definitive diagnostic uses; the value of 2.6 µg/ml had sensitivity of 40% & specificity of 85%.

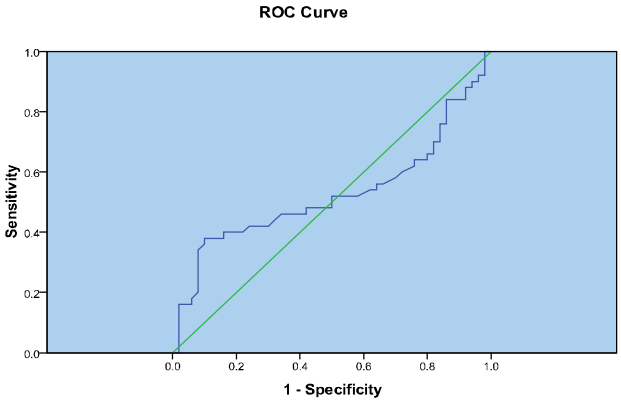


**Figure 2: Receiver Operating Characteristics (ROC) curve of irisin for prediction of hypothyroidism, Area Under Curve (AUC=0.54). Diagonal segments are produced by bites.**

## DISCUSSION:

This study is designed to answer the question whether alterations in thyroid axis hormones modify irisin levels in humans, thereby exerting a direct effect on irisin concentration. The serum irisin measurements were utilized as a support tool for the diagnosis of thyroid dysfunction. This work is executed as a specific case control study on the association between thyroid dysfunctions (hypothyroidism & hyperthyroidism) & irisin level in human. In order to avoid any interference, we have excluded both subclinical hypothyroid & hyperthyroid patients. The concern was to resolve the relations of serum of irisin levels in clearly defined groups of the thyroid abnormalities.

We found higher irisin level significantly associated with hypothyroid cases, 3.2±2.4 µg/ml ($p = 0.05$), while lower irisin level was significantly associated with hyperthyroid cases, 2.2 ± 1.1 µg/ml. Surprisingly, the irisin level in the control group was higher than hyperthyroid cases 2.5 ± 1.9 µg/ml (Table -2 & Figure -1). We have also found that there was a significant positive correlation between irisin & TSH levels. Nevertheless, there was a significant negative correlation between irisin & T3 levels, & there was a highly significant negative correlation between irisin & T4 levels (Table -4).

While we were executing this project, a recent paper was published where higher levels of irisin in hypothyroid patients was observed in comparison to the controls ( 2.77 ng/mL vs. 2.15 ng/mL; $p=0.017$ ). In addition, irisin level was independent risk factors for hypothyroidism. The irisin level was positively correlated with TSH, but negatively correlated with the FT4. Here, we have found similar correlations of irisin with TSH, this was in concordance with recent publication by Ates et al. (2016) (15). However, Ruchala et al. (2014) in an earlier publication were found contradictory results. To this end, they demonstrate that the median irisin concentration was lesser in their hypothyroid than hyperthyroid patients with a borderline statistical insignificance. Interestingly, they reported that irisin correlate negatively with TSH, but positively with FT4 serum concentrations. They postulated the degree of muscle damage, that may be influenced by thyroid metabolism, as the cause behind variations in the irisin concentration (19). Nevertheless, in a later study, they found irisin level to be significantly lower in long lasting autoimmune thyroid disease. In particular, they concluded that patients with long duration hypothyroid disease have less irisin than those with short duration (20). A recent work showed that the irisin concentrations were not altered following subclinical or interventional switches of the thyroid state (22).

Higher irisin levels were found by Samy et al. (2015) in both sedentary hypothyroid & hyperthyroid rats as compared euthyroid rats. Indeed, acute exercise in rats leads to significant elevation in serum irisin. However, the chronic training episodes failed to alter serum irisin in all thyroid states of rat's models to valuable levels. In fact, they did not found obvious association between serum irisin & metabolic abnormalities in thyroid dysfunction in rats. Notably, a significant increase in the irisin level found in hypothyroid rat group (21). Interestingly, the results are consistent with our findings in humans. Nevertheless, they found the irisin level in the hyperthyroid rats higher than the controls, while we found the values are lower than the control group. In our case, we excluded participants with positive history for strenuous physical activities & this criterion may be a confounder that strengthens indirectly our results.

No significant association found in this work between irisin & age of recruited groups of hypothyroidism, hyperthyroidism, or healthy controls. Indeed this observation is concordant to other researchers findings (30). Interestingly, Huh et al. (2014) reported that the irisin levels will be declining in older age groups above 65 years (31). In fact, the sera of young rats had higher level of irisin (32). In such context, we have excluded the possible age dependency on serum irisin levels, through selection limits ≥18 years & ≤65 years. However, we could not find any valuable correlation between irisin level & age.

On-the-other-hand, the circulating serum irisin concentrations exhibited a wide range of variations due to age dependency among

a number of studies (10,14,33,34) In the present study, the Serum irisin ELISA assay dynamic range was 0.05 - 15 µg/ml. In our hands, the mean irisin level of all study participants was 2.68 ± 1.98 µg/ml.

This study validates & highlights on the cutoff points in calculating the irisin levels together with the corresponding reference values (sensitivity & specificity) for irisin in prediction of hypothyroidism (Figure -2). The cutoff irisin level of 2.29 µg/ml was a value with validity results (52% sensitivity & 50% specificity). Regarding screening applications, the irisin value of 2.01 µg/ml was with a sensitivity of 70% & a specificity of 18%, while for the definitive diagnostic uses, a value of 2.6 µg/ml had sensitivity of 40% & specificity of 85%.

## CONCLUSIONS:

Patients with hypothyroidism have higher serum irisin level than both the hyperthyroid & the euthyroid control groups. The irisin level is correlated positively with TSH & negatively with T3 & T4. In hypothyroid patients, the irisin level was higher in those with higher WC measurements. In our hands, the high irisin level is one of the diagnostic predictors for hypothyroidism. A possible explanation for finding of high serum irisin levels in patients with hypothyroidism rather than hyperthyroidism may be due to the combination of subclinical myopathic process, increase body weight & abnormal distribution of body fat (higher WC) in this group of patients.

## LIST OF ABBREVIATIONS:

| | |
|---|---|
| **AUC** | Area Under Curve |
| **BAT** | Brown adipose tissue |
| **BMI** | Body mass index |
| **CK** | Creatine kinase |
| **FT4** | Free T4 |
| **RBG** | Random blood glucose |
| **ROC** | Receiver operating characteristic curve |
| **T3** | Triiodothyronine |
| **T4** | Tetraiodothyronine |
| **TSH** | Thyroid stimulating hormone |
| **UCP1** | Uncoupling protein 1 |
| **WC** | Waist circumference |

## DECLARATIONS

**Ethics approval & consent to participate:**

Authors declare compliance with ethical standards, according to Helsinki declaration (7th revision 2013).

**Competing interests:** no competing financial interests.

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**Authors' Contributions:**

Nazaneen Akbar Omer performed all the experiments, calculations, data analysis & wrote most of the manuscript. Fenk Bakir Maarouf assisted with sample collection & methodological/technical issues. Sarwer Jamal Al-Bajalan & Mohammed Omer Mohammed designed the study, patient's referral, statistical analysis & assisted with manuscript editing. Beston Faiek Nore conceived, supervised the project & edited the manuscript.

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