ORIGINAL ARTICLE

Beneficial effects of levothyroxine replacement therapy on leptin adiponectin ratio in patients with idiopathic primary hypothyroidism

May Hasan Abdulhadi,[1] Hayder Mutter Al-Kuraishy,[2] Ali Ismail Al-Gareeb[3]

Abstract

Objective: To assess the metabolic effects of primary hypothyroidism (PHT) on the leptin (LP), adiponectin (ADP) level and leptin adiponectin ratio (LAR), with identification of the beneficial effects of L-thyroxine (LT4) therapy on these parameters.

Methods: This case-control study was conducted at the Department of Pharmacology, College of Medicine, Mustansiriyah University, Baghdad, Iraq, from July to October 2019. This study included 62 PHT patients, of whom 27 were newly diagnosed and 35 were on LT4 therapy. There were 28 healthy controls. Anthropometric, lipid and pressure profiles were evaluated along with estimation of TSH, T3, T4, LP and ADP serum levels. SPSS version 20.00 was used for data analysis.

Results LP serum level did not significantly differ among the three groups (P=0.23), however, ADP serum level was higher in patients with PHT on LT4 therapy (77.48±9.97ng/dL) as compared to the newly diagnosed patients without LT4 (66.21±7.67ng/dL), and controls (71.40±10.72), (P=0.01). Moreover, LAR was higher in non-treated PHT (1.29±0.18) as compared to the controls (1.13±0.14), (95%CI=0.0568 to 0.2632, P=0.001) and treated PHT (1.04±0.16), (95%CI=-0.3480 to -0.1520, P=0.001). On the other hand, no significant difference was detected between healthy controls and treated PHT patients (95%CI=-0.1871 to 0.0071, P=0.07).

Conclusion: PHT is associated with poor cardio-metabolic profile and high LAR. ADP but not LP, mainly affected in patients with PHT. However LAR is better than ADP and LP in reflecting the underlying PHT-induced cardio-metabolic derangements. LT4 replacement therapy improves cardio-metabolic profile, ADP and LP serum levels with significant amelioration of LAR in PHT patients.

Keywords: Adiponectin (ADP), Leptin (LEP), Leptin adiponectin ratio (LAR), Idiopathic primary hypothyroidism (PHT), Levothyroxine (LT4). (JPMA 71: S-17 [Suppl. 8]; 2021)

Introductions

Primary hypothyroidism (PHT) is an endocrine disorder due to failure in the thyroid gland to produce thyroid hormones (THs), which are important for regulating the body metabolism. Consequently, PHT leads to obesity, fatigue, anorexia, hypertension and hyperlipidaemia.[1] THs are synthesized and release from the thyroid gland under control of thyroid stimulation hormone (TSH), and thyroid releasing hormone (TRH) which are produced by the anterior pituitary gland and hypothalamus respectively.[2] PHT is subdivided into subclinical hypothyroidism, which is associated with high TSH serum level and normal level of THs, and overt hypothyroidism, which is characterized by high TSH serum levels with low T4 (thyroxine) and T3 (triiodothyronine) serum levels.[3]

The prevalence of PHT is 1-2% worldwide, which is more common in older women compared to young and male individuals.[4] Levothyroxine sodium (LT4) is considered as the drug of choice in the management of PHT as this drug is safe, effective and well tolerated by patients and has less side effects. LT4 acts as endogenous thyroxine and after oral administration is metabolized to an active form, T3 by the action of iodothyronine deiodinase enzyme.[5]

PHT is linked with metabolic disorders due to dysregulation of adipose tissue adipocytokines like leptin and adiponectin, which have a potential role in the progression of PHT induced-cardio-metabolic disorders.[6]

Leptin (LP) is a hormone derived from adipose tissue and acts as a peripheral signal for the central nervous system (CNS). LP binds to the specific receptor in the hypothalamus to regulate food intake and energy homeostasis, leading to reduction in body weight and activation of energy expenditure.[7] There are mutual interactions between THs and LP in the regulation of body weight and energy expenditure. LP serum level is correlated positively with the body fat; body mass index (BMI) and TSH serum level.[8]

Besides, adiponectin (ADP) is an adipocyte derived

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hormone improves body energy homeostasis by promoting insulin sensitization with anti-inflammatory and anti-obesity effects.[9]

The correlation between THs and ADP is that both having various effects on the lipid and glucose metabolisms and the fact that both THs and TSH receptors are expressed on the adipose tissue.[10] THs are positively correlated with ADP serum levels; thus low ADP serum levels are suspected to occur in patients with PHT. Therefore, inflammatory reactions and neuro-metabolic disorders in PHT may be due to the reduction of ADP serum levels.[11]

The objectives of the present study was to study the potential effect of LT4 replacement therapy on the ADP and LP serum levels as well as leptin-adiponectin ratio (LAR) in patients with PHT.

Methods

This case-control study was done from July to October 2019 in the Department of Clinical Pharmacology, College of Medicine, AL-Mustansiriyah University, affiliated with the Al-Yarmouk Teaching Hospital, Baghdad-Iraq. The study was approved by Scientific and Ethical Committee Editorial Board, College of Medicine, AL-Mustansiriyah University Baghdad-Iraq. The sample size was calculated according to the population size regarding 95% confidence interval and 5% marginal error.

This study included 62 PHT patients of whom 27 were newly diagnosed patients whereas 35 patients with PHT were on LT4 therapy (n=35). There were 28 healthy controls. The blood samples were collected from all participants after an overnight fast to determine TSH, T3, T4, lipid profile, leptin and adiponectin serum levels.

The inclusion criteria were age more than 18 years and confirmed cases of PHT by thyroid function test.

Any patient having renal failure, heart failure, liver failure, thyroid disease, malignancy, secondary or tertiary hypothyroidism, pregnancy, lactation, psychiatric and mental disorders were excluded.

Weight and height of every patient was measured by means of the weight and height measuring scales for the purpose of determining body mass index (BMI); BMI= BW (kg) /Ht (m^2). Blood pressure profile, including; systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured by automated digital sphygmomanometer, then, pulse pressure (PP), and mean arterial pressure (MAP) were calculated by the following equations; PP=SBP-DBP, MAP=SBP+2 /(DBP) /3.[12]

Ten milliliters of blood samples were withdrawn through vein puncture procedure via a sterile syringe (5 ml), after an overnight fasting from all recruited patients and healthy controls. The blood samples were stored in gel tubes and centrifuged at 3000/ rpm and then stored at (-20 C°) till time of analysis.

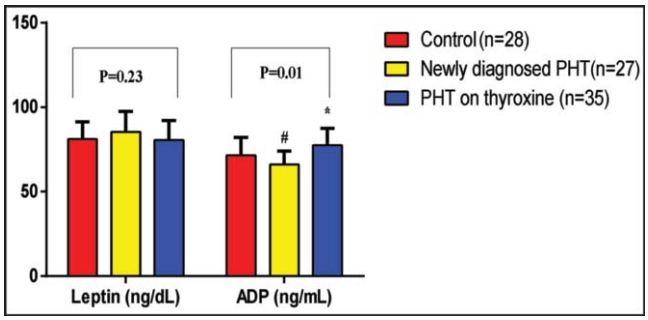
Lipid profile included triglycerides (TGs), total cholesterol (TC) and high density lipoprotein (HDL), were measured by ELISA kit methods (Abbott, A.S.A) in ARCHITECT C 4000. Whereas, low density lipoprotein (LDL), very low density lipoprotein (VLDL), Atherogenic Index (AI), cardiovascular risk index (CVRI) and cardiac risk ratio (CRR) were measured by specific equations according to a previous study.[13] Leptin and adiponectin serum levels were measured by ELISA kit methods (MyoBio source, USA.) .

Data was analyzed using SPSS 20, and presented as mean ± standard deviation (SD) and the variables were tested by using unpaired student t-test between the controls and the treated groups. One way analysis of variance (ANOVA) with post-hoc test was used to scrutinize the significance of differences among the groups. Level of significance was regarded when P<0.05.

Results

BMI was higher in the newly diagnosed patients without LT4 therapy compared to the patients on LT4 therapy (P=0.03). Blood pressure profile was higher in patients with PHT compared to the controls (P=0.0001), and it was higher in the newly diagnosed patients as compared to PHT on LT4.

Biochemical profile: Lipid profile was higher in newly diagnosed patients with PHT compared to the controls (P=0.0001) with exception of HDL-c level, which did not significantly differ among groups (P=0.06). Moreover,



Data are presented as mean ±SD, ANOVA test.
*** P <0.01 compared to untreated group and control.**
 # P<0.05 compared to the control.

Figure-1: leptin and adiponectin level in newly diagnosed patients with primary hypothyroidism with or without thyroxine therapy compared with control.

Table-1: Metabolic profile in patients with primary hypothyroidism compared with controls..

Variables	Controls (n=28)	Newly diagnosed PHT (n=27)	PHT on thyroxine (n=35)	P
BMI(kg/m^2)	31.61±3.72	34.81±5.70	31.75±5.45*	0.03
SBP(mmHg)	111.64±12.85	145.61±15.80#	128.42±13.91*¶	0.0001
DBP(mmHg)	75.93±9.75	97.42±11.73#	81.72±10.81*	0.0001
PP(mmHg)	35.71±6.94	48.19±7.56#	46.70±8.52¶	0.0001
MAP(mmHg)	87.83±8.63	113.48±12.96#	97.29±11.86*¶	0.0001
TC (mg/dL)	143.67±13.27	176.43±14.88#	150.62±14.14*	0.0001
TG(mg/dL)	132.25±16.54	184.00±13.85#	139.47±16.73*	0.0001
HDL-c(mg/dL)	39.29±12.59	32.62±3.81	35.17±12.04	0.06
non-HDL-c	104.38±9.07	143.81±13.81#	115.45±11.73*¶	0.0001
LDL(mg/dL)	77.90±8.52	107.00±13.85#	87.60±11.71*¶	0.0001
VLDL(mg/dL)	26.45±12.61	36.85±9.44#	27.89±9.73*	0.0001
AIP	0.161±0.01	0.391±0.04#	0.238±0.03*¶	0.0001
CRR	3.65±1.89	5.40±1.88#	4.28±1.07*	0.03
CVRI	3.36±1.08	5.64±2.31*	3.96±1.67*	0.04

Data are presented as mean ±SD, ANOVA test and Tukey HSD Post-hoc Test, BMI: body mass index; WHR: waist hip ratio, BFM: body fat mass, BF% body fat percentage, SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; TC: total cholesterol; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; AI: atherogenic index, CRR: Cardiac Risk Ratio, CVRI: cardiovascular risk index.

*P <0.05 compared to untreated group.

# P<0.05compared to the control.

¶ P<0.05compared to the control.

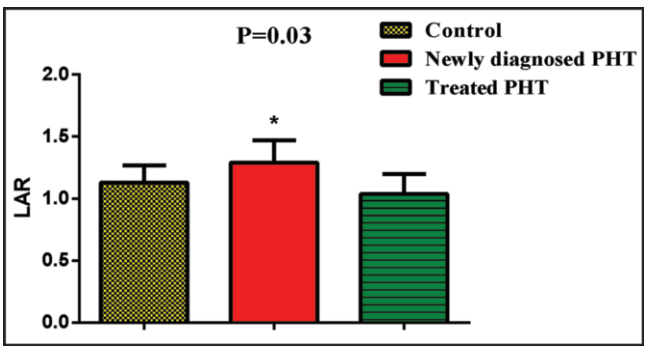
Table-2: Thyroid function in patient with idiopathic primary hypothyroidism with or without thyroxine therapy.

Hormonal levels	Control (n=28)	Newly diagnosed PHT (n=27)	PHT on thyroxine (n=35)	P
T4 μg/dL	90.53±12.00	66.19±10.57	97.62±19.54*	0.001
T3 ng/dL	1.58±0.38	1.34±0.30#	1.61±0.32*	0.005
TSH mIU/L	2.27±0.76	10.17±6.02#	2.53±1.62*	0.001

Data expressed as mean ± SD, ANOVA test and Tukey HSD Post-hoc Test, *P<0.05 compared to newly diagnosed patient with primary hypothyroidism, # P<0.05 as compared with the controls. PHT: primary hypothyroidism; T4: thyroxine; T3: triiodothyronin; TSH: thyroid stimulating hormone.

atherogenic index (AIP) was higher in patients with PHT compared with the controls (P=0.0001), however, it was higher in patients with PHT (0.391±0.04) as compared with patient with PHT on LT4 therapy (0.238±0.03), (P=0.0001).

Furthermore, cardiac risk ratio (CRR) and cardiovascular risk index (CVRI) were higher in patients with PHT compared with the controls (P=0.03) and (P=0.04) respectively. Both CRR and CVRI were lower in patients with PHT on LT4 therapy as compared with newly diagnosed patients with PHT, (Table-1).



*** P<0.05 compared to the treated group or control.**
Treated versus control not significant P=0.07, LAP: leptin/adiponectin ratio.

Figure-2: Leptin- adiponectin ratio (LAR) in patients with primary hypothyroidism compared with the controls.

A significant difference in thyroid function parameters were noted as, serum T4 level which was higher in patients on LT4 therapy (97.62±19.54 μg/dL) as compared to 66.19±10.757 μg/dL in the newly diagnosed PHT patients (p=0.001) and controls 90.53±12.00 μg/dL.

A significant difference was also seen in serum T3 levels between PHT patients on LT4 therapy (1.61±0.32 ng/dL) and newly diagnosed PHT patients (1.34±0.30 ng/dL) as well between newly diagnosed and healthy controls (1.58±0.38 ng/dL) (p=0.005). Moreover, TSH value also significantly differed between newly diagnosed patients (10.17±6.02) as compared to LT4 therapy group (2.53±1.62) and control group (2.27±0.76), (p=0.001), (Table-2).

Leptin serum level was not significantly different among groups (P=0.23), however, ADP serum level was higher in

patients with PHT on LT4 therapy (77.48±9.97ng/dL) as compared with the newly diagnosed patients without LT4 therapy (66.21±7.67ng/dL), and controls (71.40±10.72), (P=0.01), (Figure-1).

Moreover, Leptin-adiponectin ratio (LAR) was higher in non-treated PHT (1.29±0.18) as compared to the controls (1.13±0.14), (95%CI=0.0568 to 0.2632, P=0.001) and treated PHT (1.04±0.16), (95%CI=-0.3480 to -0.1520, P=0.0000). On the other hand, no significant difference was seen between healthy controls and treated PHT patients (95%CI=-0.1871 to 0.0071, P=0.07), (Figure-2).

Discussion

In the present study LT4 therapy improved TSH and THs levels, both T3 and T4 serum levels were normalized with significant reduction in serum TSH levels as LT4 is regarded the prototype first line therapy in the management of PHT.[4] PHT causes an increase in BMI, as PHT is highly correlated with the development of obesity.[11] However, our data showed that, there was a significant difference in BMI, which was higher in newly diagnosed as compared to patients on LT4 therapy and healthy controls. This has been documented in a recent study that reported the association between PHT with central adiposity and high body fat mass, which is reversed by LT4 therapy.[14] In addition, our study showed a positive association between PHT and hypertension, thus SBP, DBP, PP and MAP were higher in the newly diagnosed patients as compared to the patients on LT4 therapy. This was shown by a previous meta-analysis study, which demonstrated that LT4 therapy reduces systemic hypertension.[15] Different studies point out that systemic hypertension is one of the most common secondary complication of PHT, since different pathological factors contribute into the pathogenesis of hypertension in PHT including development of arterial stiffness, reduction of vascular elasticity, peripheral vasoconstrictions due to down-regulation of $\beta 2$ adrenoceptors and un-opposing effect of $\alpha 1$ adrenoceptors. All these factors are reversed by LT4 therapy.[16]

Moreover, findings of our study confirmed that newly diagnosed patients with PHT were associated with hyperlipidaemia, which was mitigated following LT4 therapy. However, HDL-c serum level did not differ significantly in the newly diagnosed patients with PHT compared with PHT on LT4 therapy. It has been reported that PHT induced-hyperlipidaemia develops due to reduction of LDL receptors and induction of lipogenesis.[17] Therefore, LT4 therapy improves lipid profile due to degradation of LDL-c and increasing the expression of LDL-c receptors. These facts might explain the occurrence of hyperlipidaemia in patients with PHT which is ameliorated by LT4 therapy as in the present study. Indeed, high TSH serum, low THs level and associated hyperlipidaemia contribute mutually into the acceleration and augmentation of cardiac risk ratio, cardiovascular risk index, atherogenicity and cardiovascular complications. Definitely, high TSH serum levels lead to induction of endothelial dysfunction, impairment of cardiac contractility and coronary heart disease independent of THs levels. This effect is mediated by cardio-myocyte TSH-receptors. Thus, obesity, hypertension, hyperlipidaemia and cardiovascular complications are associated with reduction in ADP serum levels and increased LAR which contributes to the metabolic syndrome.[18]

Both LP and ADP are thought to play imperative roles in the regulation of hypothalamic-pituitary (HPT) axis and metabolic homeostasis. LP acts on the hypothalamus, increased food intake and positively correlates with the degree of body obesity.[19] On the other hand, ADP is involved in the regulation of metabolic homeostasis through activation of fat oxidation and reduction of fatty acids and triglycerides. Nevertheless, ADP level is paradoxically reduced in patients with obesity and metabolic syndrome.[20] Therefore, LAR serves as a metabolic biomarker superior to ADP or LP alone in the assessment of metabolic profile in PHT.

Moreover, LP and ADP are critical pathophysiological factors associated with metabolic syndrome and obesity, so any disturbances in the levels of LP and ADP may cause fat accumulation due to increase in the appetite with reduction of energy expenditure.[21] In PHT, patients have an increased tendency to obesity, lipid disturbances and hypertension. All of these factors are associated with increased risk of metabolic syndrome and cardiovascular diseases. Several studies showed that LAR is an influential diagnostic tool of metabolic syndrome.[22]

According to the present data, LAR was higher in newly diagnosed patients with PHT compared to PHT on LT4 therapy, and there was no significant difference among controls and patients on LT4. A previous cross-sectional study indicates that, high TSH levels in euthyroid individuals with metabolic syndrome was associated with an increase of LAR, which is a proposed biomarker for adipocyte dysfunction and the development of metabolic abnormalities.[23] Therefore, high LAR in PHT indicates underlying metabolic disturbances which was observed in the current study. LAR was significantly correlated with high TSH serum levels. High LP and low ADP serum levels in the present study were correlated with hyperlipidaemia and atherogenic index. Thus, high LAR in the present study reflects PHT induced-cardio-metabolic disturbances.[24] Following LT4 replacement therapy, LAR was reduced to a value comparable to that of healthy controls. This

improvement in LAR might be due to the reduction of TSH serum levels and amelioration of cardio-metabolic profile as documented by a recent study.[25]

The present study had several limitations which included a small sample size, and pro-inflammatory cytokines that augmented in PHT not being evaluated. Though, the present study provided a clue in connotation between PHT patients and LAR. Large prospective clinical trials are warranted in this regard to observe and confirm the dose-dependent effect of LT4 therapy on LAR in patients with PHT.

Conclusion

PHT is associated with poor cardio-metabolic profile and high LAR. ADP but not LP is mainly affected in patients with PHT, however LAR is better than ADP and LP in reflecting the underlying PHT-induced cardio-metabolic derangements. LT4 replacement therapy improves cardio-metabolic profile, ADP and LP serum levels with significant amelioration of LAR in PHT patients.

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Conflict of Interest: None.

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