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Examination of the plasma amino acid profiles in Hashimoto's thyroiditis patients

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Abstract

Aim: The aim of our study is to determine the possible role of plasma amino acids before and after treatment in Hashimoto's thyroiditis (HT) patients, to reveal the profile of amino acid metabolites in the development of thyroid autoantibodies and thyroid disease.

Methods: Thirty HT patients and thirty healthy individuals were included in this study. Demographic data of the patients were recorded. Plasma amino acid profile was measured with 8045 LC-MS/MS device. Multivariate statistical analysis of the studied parameters was performed.

Results: In our study, average levels of alanine, arginin, aspartic acid, citrulline, glutamine, glutamic acid, glycine, histidine, leucine, isoleucine, alloisoleucine, lysine, methionine, phenylalanine, proline, serine, tryptophan, tyrosine, valine, alpha amino pimelic acid, anserine, argininosuccinic acid, beta and gamma amino butyric acid, 1-3 methylhistidine, hydroxy proline, cystine, homocystine, ethanolamine, 5-OH-tryptophan alpha amino adipic acid and taurine were found to be significantly lower in HT group who did not receive treatment than the control group (p<0.05). Other amino acids levels such as arginine, citrulline, glutamic acid, glycine, histidine, leucine, isoleucine, lysine, methionine, phenylalanine, proline, tryptophan, tyrosine, valine, alpha amino adipic acid, alpha amino pimelic acid, anserine, argininosuccinic acid, beta and gamma amino butyric acid, hydroxyproline, cystine, homocystine, allo-isoleucine, ethanolamine, 5-oh-trp and taurine were found to be significantly low at post treatment. The except was serine which its level was significantly higher than the control group (p<0.001).

Conclusion: In our study, the amino acid profile may be a potential biomarker in diagnosis, therapy, follow-up and prognosis of HT. This study also provides the relationship between amino acid profiles and HT. More basic studies are needed for the real mechanism of amino acids in elucidation of HT.

Keywords: Hashimoto's thyroiditis, thyroid disease, metabolomics, plasma amino acids, LS-MS/MS

Introduction

Hashimoto's thyroiditis is a common thyroid hormone disorder. The incidence of overt hypothyroidism and subclinical hypothyroidism is between 0.2% and 5.3% in the general population and increases in female gender and older age (1). In addition to genetic factors, environmental factors such as nutrition also play an important role in the development of HT (2). It is a chronic autoimmune thyroid disorder characterized by the production of thyroid autoantibodies. Other main features of HT include infiltration of lymphocytes and destruction of thyroid tissue, which often leads to hypothyroidism (3). This disease predominantly affects the female population and is considered one of the most common endocrine disorders (3). The estimated incidence of HT is 350/100,000 for women and 80/100,000 per year for men (3). It is most commonly diagnosed in women between the ages of 30 and 60. High iodine intake (median urine iodine concentration≥ 300μg/L), especially in regions with sufficient iodine supply, is one of the most well-known factors that increase the incidence of HT (4). They are suggested to be the most important risk factors for the development of HT, and alcohol intake has also been suggested to reduce the risk of HT. Other dietary factors are also considered potential environmental modifiers of the clinical presentation of HT (5). Food can be considered an important environmental factor playing a role in the development of HT (6). Protein is an essential macronutrient in the human body and has various physiological functions. Amino acids are components of protein, and the content of amino acids directly affects the quality of food proteins (7). Modern nutritional theory research shows that deficiency or excess of amino acids affects HT (8).

Hypothyroidism causes systemic inflammation at the micro level in the body. This inflammation has been associated with metabolic diseases and some types of cancer (9). In studies, parameters such as C-reactive protein, tumor necrosis factor-alpha (TNF-alpha), total leukocyte count, and erythrocyte sedimentation rate can be used to determine the level of systemic inflammation (10). Additionally, the neutrophil-lymphocyte ratio has begun to be used to determine the systemic inflammatory response (11, 12). It has also been shown in previous studies that, as values that can be measured by hemogram, they serve as practical and valuable markers in determining the clinical course or severity of other diseases that progress with autoimmune and chronic inflammation and can be used to determine prognosis (13).

The aim of this study is to analyze plasma-free amino acid concentrations in HT patients using metabolomics, evaluate the ability of HT innate immune responses to reveal how the disease develops, and show that amino acid balance. Changing in amino acid availability and balance may be useful in determining treatment policies.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Harran University Faculty of Medicine with the letter numbered HRÜ/23.03.31 and dated 20.02.2023. Signed informed consent forms were obtained from all patients, and they met all criteria.

Patient Selection

A total of 30 patients who applied to the endocrinology clinic of Harran University and were diagnosed with Hashimoto's thyroiditis were selected for this study. Clinically, patients with Hashimoto's thyroiditis were selected based on elevated serum thyroid stimulating hormone levels, high levels of antithyroid peroxidase antibodies, and the presence of "echogenicity, heterogeneity, hypervascularity, and small cysts" detected on ultrasound (14). Our HT patient group consisted of 30 newly diagnosed patients (20 females and 10 males) who had never received treatment before, and the mean age of these patients was (36.75±11.93) years.

Study Protocol

Blood samples were taken from these patients before and after treatment. Our healthy control group consisted of 30 individuals (18 females and 12 males). The mean age of these individuals was 38.00±7.46 years who applied to the endocrinology clinic and were not diagnosed with Hashimoto's thyroiditis and did not have any autoimmune or chronic diseases. Plasma levels of thyroid stimulating hormone, triiodothyronine, thyroxine, thyroid peroxidase antibody, and thyroglobulin antibody were measured in HT patients and controls using the Atellica device (Elabscience, Houston, Texas, TX, USA).

For amino acid analysis, all plasma samples were obtained using EDTA as an anticoagulant. Plasma was prepared by centrifuging at 3000 rpm for 15 min at 4 °C and then stored at -80 °C until analyzed. Plasma amino acid profiles in patient and control groups were measured on the 8045 LC-MS/MS instrument. 350 µl and 25 µl of internal standards were added to the cell pellets and mixed for 5 seconds. They were centrifuged at 1000 g for 5 minutes and 150-200 µl of supernatants were taken, placed in insert vial bottles, and run three times on the 8045 LC-MS/MS instrument. The study design is graphically illustrated in Figure 1.

Statistical analysis

Analyses were performed by using SPSS 26.0 software. (IBM Inc., Armonk, New York, USA).

Descriptive statistics are given as minimum, maximum, and mean standard deviation. Shapiro-Wilk test was preferred to check normality. Levene's test was used to determine whether the samples were suitable. It has equal variances. Welch's one-way test ANOVA was combined with Games-Howell multiple post-hoc comparison test-Risons in different groups were used to perform pairwise comparison. Korean relationships were determined using the Pearson correlation relationship between variables. Values greater than 0.05 were considered not statistically significant.

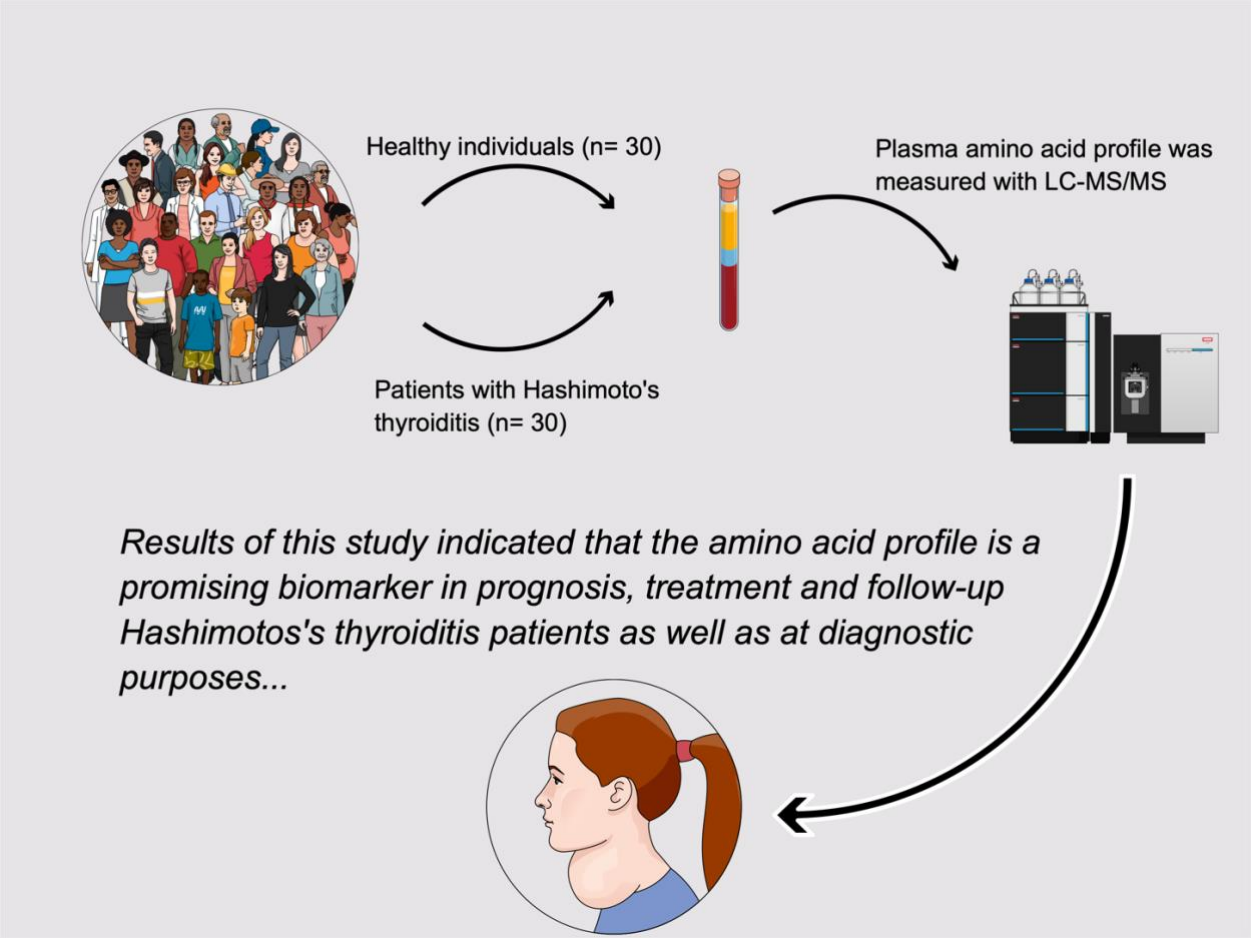

Figure 1. Schematic representation of the step-by-step procedure.

Results

The serum TSH, FT3, FT4, anti-TPO, anti TG levels of 60 individuals participating in the study are shown in Table 1. The age and gender distributions between the groups were similar (p=0.557) and (p=0.075) respectively.

From amino acids, glutamine, glutamic acid, anserine, beta-amino butyric acid, and gamma amino butyric acid levels were found to be significantly lower before treatment than after treatment (p<0.05; Table 2). The amino acids; alanine, arginine, aspartic acid, citrulline, glutamine, glutamic acid, histidine, leucine, isoleucine, alloisoleucine, lysine, methionine, phenylalanine, proline, serine, tryptophan, tyrosine, valine, alpha amino pimelic acid, anserine, argininosuccinic acid, beta and gamma amino butyric acids, 1-3 methyl histidine, hydroxyproline, cystine, homocysteine, ethanolamine, 5-OH-trp, and taurine levels are significantly lower than the control group, and the alpha-amino adipic acid level is significantly higher than the control group was found (p<0.05; Table 2).

Among the amino acids, arginine, citrulline, glutamic acid, glycine, histidine, leucine, isoleucine, lysine, methionine, phenylalanine, proline, tryptophan, tyrosine, valine, alpha amino adipic acid, alpha amino pimelic acid, anserine, argininosuccinic acid, beta and gamma (amino butyric acid), hydroxyproline, cystine, homocysteine, ethanolamine, 5-oh-trp and taurine levels were found to be significantly lower and serine levels which were significantly higher after treatment than in the control group (p<0.05; Table 2).

Table 1. Mean and significance values of HT patients before treatment and control groups

	HT patients group Mean ± SD	Control group Mean ± SD	*p*-value
TSH (mU/L)	12.27±2.69	2.48±0.55	<0.001
FT3 (pmol/L)	2.36±0.48	4.978±0.31	<0.001
FT4 (nmol/L)	0.79±0.71	1.66±0.26	<0.001
Anti-TPO (U/mL)	769.56±168.75	27.33±6.57	<0.001
Anti-Tg (U/mL)	356.54±39.78	2.62±1.49	<0.001

(TSH) Thyroid-stimulating hormone; (FT3) Free T3 (triiodothyronine), FT4 free T4 (thyroxine); Anti-TPO (thyroid peroxidase antibody); Anti-Tg (thyroglobulin antibody)

Table 2. Mean and significance values of HT patients before treatment groups, after treatment and control groups

Parameters (µmol/L)	Control Groups Mean±SD	Before Treatment Mean±SD	After Treatment Mean±SD	Before and After Treatment *p*-value	Before and control groups *p*-value	After Treatment and control groups *p*-value
Alanine	389.57±41.09	274.73±23.43	341.24±36.97	0.418	0.044	0.036
Arginine	173.61±35.48	68.49±20.42	164.02±27.93	0.685	0.001	0.001
Asparagine	43.93±7.42	36.20±6.39	36.71±12.62	0.930	0.116	0.073
Aspartic Acid	60.43±12.46	10.49±3.83	52.64±9.24	0.562	0.001	0.001
Citrulline	43.51±11.09	19.04±4.21	43.85±12.06	0.969	0.001	0.001
Glutamine	190.49±36.23	93.37±24.13	139.17±35.15	0.009	0.018	0.039
Glutamic acid	432.87±73.00	78.31±26.99	300.48±32.74	0.050	0.001	0.001
Glycine	285.11±36.28	198.01±22.47	275.60±48.56	0.861	0.027	0.034
Histidine	102.41±36.57	57.52±12.48	95.76±16.30	0.595	0.001	0.001
Leucine	162.21±43.54	95.27±15.06	139.72±12.03	0.278	0.004	0.001
İsoleucine	126.20±32.76	59.96±15.95	115.62±24.68	0.441	0.001	0.001
Alloisoleucine	2.78±1.06	0.36±0.019	2.64±0.55	0.346	0.001	0.144
Lysine	226.29±60.14	132.56±36.88	199.56±34.30	0.173	0.001	0.001
Methionine	24.25±6.27	7.16±2.19	7.00±2.57	0.695	0.001	0.001
Ornithine	85.84±23.54	67.43±18.42	67.51±12.88	0.346	0.504	0.697
Phenylalanine	122.96±28.29	51.10±10.20	103.09±22.90	0.156	0.001	0.001

Proline	329.05±143.47	155.49±40.28	262.60±60.19	0.126	0.001	0.001
Serine	207.18±62.36	130.52±31.19	221.86±36.90	0.530	0.001	0.001
Theronine	137.00±41.58	132.52±37.08	123.64±44.84	0.482	0.735	0.513
Tryptophan	86.59±20.08	56.44±14.93	79.61±15.40	0.619	0.034	0.026
Tyrosine	126.79±58.97	68.62±16.83	113.44±34.98	0.875	0.001	0.001
Valine	276.92±76.03	174.70±47.57	272.89±88.83	0.889	0.003	0.001
Alpha-amino adipic acid	0.39±0.17	0.94±0.57	0.37±0.21	0.875	0.001	0.001
Alpha-amino pimelic acid	0.57±0.32	0.404 ±0.12	0.56±0.22	0.963	0.001	0.001
Anserine	9.45±2.83	2.11±1.31	5.74±1.86	0.007	0.001	0.001
Argininosuccinic acid	0.19±0.11	0.16±0.033	0.16±0.017	0.326	0.011	0.177
Alpha-amino butyric acid	14.82±6.40	13.32±6.12	15.12±9.77	0.530	0.486	0.867
Beta amino isobutyric acid	7.74±3.72	4.46±1.82	2.66±0.89	0.050	0.001	0.001
Gamma amino butyric acid	82.73±22.40	45.39±16.70	40.89±10.70	0.001	0.001	0.001
Beta-alanine	4.20±107	3.04±1.05	3.79±1.56	0.624	0.119	0.126
Cystathionine	0.29±0.12	0.12±0.02	0.15±0.030	0.182	0.944	0.478
Thiaproline	0.07±0.03	0.08±0.02	0.04±0.01	0.141	0.791	0.084
1-Methylhistidine	3.86±1.51	1.30±0.037	2.14±0.40	0.117	0.001	0.616
3-Methylhistidine	1.97±0.30	0.66±0.15	1.91±0.99	0.433	0.003	1.000
Hydroxylysine	0.15±0.014	0.08±0.06	0.10±0.08	0.789	0.461	0.098
Hydroxyproline	47.77±21.52	25.67±10.39	36.80±8.10	0.124	0.003	0.003
Cystine	46.55±24.44	41.00±11.91	40.92±13.26	0.480	0.001	0.001
Homocysteine	0.17±0.018	0.01±0.01	0.01±0.01	1.000	0.001	0.001
Serotonin	0.29±0.030	0.10±0.025	0.10±0.012	0.066	0.168	0.001
Histamine	0.05±0.03	0.02±0.002	0.04±0.003	0.261	0.001	0.001
Ethanolamine	38.77±23.00	7.26±6.21	29.37±15.76	0.255	0.001	0.001
5-OH-Tryptophan	0.41±0.21	0.04±0.009	0.25±0.19	0.075	0.001	0.001
Taurine	258.82±39.75	78.29±37.28	245.61±49.4	0.576	0.001	0.001

Discussion

The effect of the amino acid profile on HT at the metabolomic level and a literature review on this subject have been conducted. Genetic factors and environmental factors also play an important role in the development of HT (15). HT is a chronic autoimmune thyroid disorder characterized by the production of thyroid autoantibodies against thyroid peroxidase and thyroglobulin (16). Tyrosine and phenylalanine deficiency cause changes in the levels of thyroid hormones (17). Other main features of HT include infiltration of lymphocytes and destruction of thyroid tissue, often leading to hypothyroidism (18). The disease is a result of advanced T cell activation, and it is the most common chronic autoimmune thyroid disease characterized by painless goiter and high levels of blood thyroid antibodies (19, 20).

HT disease is more commonly observed in older women (4). It predominantly affects the female population in the age group of 30-60 years (2). Hypothyroidism is considered an important risk factor for heart diseases development, especially atherosclerosis (21). It was also reported that the rate of hypothyroidism is higher in patients with coronary heart disease, and regular hypothyroidism (21). Endothelial dysfunction and impaired relaxation of smooth muscle cells are thought to be responsible for cardiovascular problems in hypothyroidism (7).

In recent years, it has been reported that amino acid deficiency may cause autoimmune diseases. Ostrowska et al. in their study, stated the incidence of goiter in 55% of malnutrition cases, while 18.6% of same cases presented with hypothyroidism (22). Conversely, there is a correlation between the thyroid gland and obesity. Hypothyroidism causes the body's metabolism to decrease, resulting in weight gain. However, this does not always mean that a thyroid problem causes obesity, nor that an overweight person is experiencing hypothyroidism (12, 19). Most of the individuals with thyroid disease have normal thyroid function tests or subclinical hypothyroidism. The cause of goiter in these patients is lymphocytic infiltrations that enlarge the thyroid tissue (23).

Tyrosine is necessary for the synthesis of thyroxine produced by the thyroid gland (23). Deficiency of tyrosine and phenylalanine causes changes in the levels of thyroid hormones (23). In our study, plasma tyrosine and phenylalanine levels were found to be statistically significantly lower in HT patients before and after treatment compared to the control group (p<0.001; Table 2). Although all these amino acids are important for metabolism and protein synthesis, their relationship with HT has recently attracted attention (24, 25).

The amino acid glutamine is an important carbon source for adenosine triphosphate (ATP) production, nucleotide and protein biosynthesis, and regulation of redox balance (26). Glutamate is synthesized from glutamine by glutaminase in brain neurons. After glutamate is released from the synaptic terminal, it is taken up into astrocytes, where it is converted to glutamine-by-glutamine synthetase; glutamine is then transported to neurons and reused (26, 27). This is an important component of the neurotransmission system. In our study, a statistically significant decrease was observed in glutamate and glutamine levels (p<0.001; Table 2). Based on these findings, it can be hypothesized that the glutamate-glutamine cycle of HT patients is impaired, and the enzymes associated with this cycle are irregular.

In terms of autoimmunity, increased tissue destruction and increased amino acid release are the reasons for the increase in a factor contributing to the prevalence of the disease (27). Neoplasm cells require some amino acids such as glutamine, glycine, aspartic acid, and serine for DNA synthesis, new vessel formation, proliferation of proteins, and synthesis of hormones such as growth factors or growth promoters (28). The amino acid aspartate enters the urea cycle and helps produce glutamine and urea, among other reactions, reducing ammonia levels in the environment. Most of this activity occurs in the liver, kidneys, and muscles (29, 30).

Taurine is one of the few amino acids that are not used in protein synthesis (21). It plays a role in regulating intracellular free calcium concentration and is one of the few amino acids not incorporated into proteins (8). In our study, plasma taurine levels were found to be statistically significantly lower in HT patients before and after treatment and compared to the control group (p<0.001; Table 2). The researchers reported that taurine is known for its alleged effects as an energy-giving and anti-fatigue compound. It can be assumed that taurine, an amino acid that acts as a neurotransmitter, is impaired in the regulation of skeletal muscle contractile function, and its ability to increase exercise capacity and performance while reducing exercise-induced DNA damage is impaired (28, 29).

Arginine is converted to ornithine and urea by arginase enzyme (31). In our study, plasma arginine levels in HT patients were found to be statistically significantly lower before and after treatment and when compared with the control group. In this case, the effect of the arginase enzyme in HT plasma can be investigated in future studies (32).

Methionine has a role in cellular reversible oxidation and reduction reactions (32). In our study, plasma methionine was determined to be significantly lower in HT patients compared to pre-treatment, post-treatment, and normal control groups.

Lysine affects protein production in muscles and bones, and lysine deficiency causes chronic fatigue, irritability, hair loss, anemia, susceptibility to infection, recurrent cold sores, and metabolic disorders (24). In our study, plasma Lysine levels were found to be statistically significantly lower in HT patients before and after treatment and compared with the normal control group. They showed that lysine degradation pathways of HT patients have an effect on different clinical stages of HT (24, 25). It has been shown that reactive oxygen species

(ROS) produced at high levels during exercise may contribute to muscle fatigue and exercise-induced muscle damage. Carnosine has been shown to reduce oxidative stress by acting as an antioxidant during exercise. In our study, plasma carnosine and histidine levels were found to be statistically significantly lower in HT patients before and after treatment compared to the normal control group. It has been shown that reactive oxygen species (ROS) produced at high levels during exercise may contribute to muscle fatigue and exercise-induced muscle damage, and histidine supplementation, which is a rate-limiting precursor for carnosine synthesis, where free radicals are formed in HT patients, has been shown to improve tissues and increase training quality (34, 35).

Amino acids play important physiological roles in living cells. Some amino acid changes in the blood are specific to autoimmune disorders. Other amino acid levels such as citrulline, leucine, isoleucine, lysine, methionine, phenylalanine, proline, tryptophan, valine, alpha amino adipic acid, alpha amino pimelic acid, anserine, argininosuccinic acid, beta and gamma amino butyric acid, hydroxyproline, cystine, homocysteine, allo-isoleucine, ethanolamine, and 5-oh-trp were found to be significantly lower after treatment compared to the control group. However, alpha amino adipic acid levels were found to be statistically significantly higher (p<0.001, Table 2). Since the roles of these amino acids in metabolic pathways have not been fully elucidated, it is not possible to produce a thesis about how they participate in the pathophysiological process. In our study, it was found that FT4 values were decreased and FT3 values were increased in HT patients before treatment, and this was statistically significant when compared with the healthy control group. Decreased values of FT4 and increased values of FT3 reveal Hashimoto's disease (24). It was also found in our study that plasma levels of glycine, aspartic acid and serine were significantly lower in HT patients before. These data indicate that amino acid metabolism has important physiological roles and support the idea that deficiency of some blood amino acid levels may result in the development of autoimmune disorders. Long-term studies in larger populations are necessary to confirm the potential role of specific amino acids in diagnosing thyroid diseases.

Conclusion

Amino acid profile values were significantly lower in patients with Hashimoto's thyroiditis than in healthy controls. Amino acid metabolism has been associated with several pathological conditions, including HT disease. Amino acid profiles may be useful markers in the diagnosis, prognosis, monitoring therapy, and follow-up of HT disease.

Disclosures

Ethical Approval: Ethics committee approval was received for this study from the Harran University, Faculty of Medicine, Local Ethics Committee, in accordance the World Medical Association Declaration of Helsinki, with the approval number: 2023-23.03.31.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.B.; Design – M.B., M.A.E.; Supervision – M.A.E.; Materials – M.B., N.B.; Data collection &/or processing – M.B., N.B.; Analysis and/or interpretation – M.A.E., N.B.; Literature search – M.B.; Writing – M.B.; Critical review – M.A.E, N.B.

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