

Evaluation of Serum Level of Zinc and Biotin in Patients with Alopecia Areata

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Abstract

Foundation: Alopecia areata is a non-scarring going bald condition that can happen and repeat in male or female at any age and on any piece of hair-excepting regions. Zinc has a significant part in different metabolic pathways and cell capacities. Biotin engaged with fundamental physiological capacities like unsaturated fat combination, amino corrosive catabolism, and gluconeogenesis. The point of the current examination was to assess serum zinc and biotin level in patients with AA. **Subjects and strategies:** This investigation was led on sixty patients experiencing AA. Notwithstanding sixty clearly solid people of coordinated age, sex and BMI as a benchmark group. Serum level of zinc and biotin were estimated in the two gatherings. **Results;** Results of the current investigation demonstrated huge contrasts with respect to serum zinc and biotin levels in AA patients when contrasted with control gathering. there was a noteworthy relationship between's serum zinc and serum biotin. **Conclusion:** zinc and biotin serum levels were lower in AA patients contrasted with controls, which may assume significant function in the pathogenesis of the sickness. What's more, this examination may give significant insights to help the improvement of new restorative systems for patients with AA.

Keywords: C-reactive protein, Neutrophil, Spontaneous bacterial peritonitis, Chronic liver.

1.Introduction

Alopecia areata (AA) is one of the most widely recognized skin ailments, prompting interminable and backsliding balding. The beginning might be at any age and there is no known race or sexual orientation prevalence. It generally presents as patches of going bald on the scalp yet any hair-bearing skin may likewise be included [1].

Zinc is a fundamental minor component that is important for development and advancement at all phases of life [2]. Zinc assumes a key part in physical development and improvement, working of the resistant framework, conceptive wellbeing, tactile capacity and neurobehavioral advancement. It has been assessed that around 33% of the world's human populace have counts calories lacking in zinc [3]. Mellow zinc inadequacy is related with discouraged resistance, hindered taste and smell, beginning of night visual deficiency, and diminished spermatogenesis. Serious zinc lack is described by seriously discouraged invulnerable capacity, regular diseases, the runs, and alopecia [4].

Biotin (otherwise called nutrient B7 or nutrient H) is a water-dissolvable nutrient and one of the supplements that are exceptionally subject to bacterial creation. It is a fundamental supplement for human wellbeing, especially skin wellbeing, and biotin lack is related with serious dermatologic conditions, including balding [5]. Because of its moderately ease and bounty of accessibility in restorative items, biotin has become the new pattern for shoppers wishing to have longer, more beneficial hair and nails [6].

Taking into account these focuses, we planned this examination to discover the relationship among zinc and biotin levels and alopecia areata.

2.Patient and method

This case control study was led on sixty patients whining of alopecia areata, and sixty age, sex and BMI coordinated sound volunteers. Patients were selected from Outpatient Clinics of Dermatology, Venereology and Andrology Department of Benha University Hospitals during the period from April 2018 to February 2019.

2.1 Inclusion criteria

The inclusion criteria for patients with AA were: being over 18 years of age, and willing to participate in the study.

2.2 Exclusion criteria

Any patient with any of the following condition was excluded from this study:

- Past history of topical treatment less than two weeks and/or systemic treatment less than one month.
- Patients taking zinc or biotin supplements.
- History of active malignancy or taking immunosuppressive treatment.
- Patients with a history of any systemic disease e.g. chronic liver or renal diseases, and autoimmune diseases.
- Physical disability and any neurological disorder.

2.3 Administrative design

This study was approved by the Research Ethical Committee of Benha Faculty of Medicine.

2.4 Ethical consideration

Before taking blood samples, a written informed consent was taken from each patient and normal volunteers in the control group.

All participants were divided into two groups

- Group A: sixty patients with an AA.
- Group B: sixty age, sex and BMI matched volunteers as controls group.

2.5 Methods

All patients were subjected to the following

Full history taking

- Personal history: Name, age, occupation, residence and smoking or special habit of medical importance.
- Present history: onset, course and duration of AA.
- Past history: history of medications (type and duration), associated systemic and/or autoimmune diseases, endocrinal problems.
- History of previous treatment of AA (type, dose and duration).
- Family history of AA.

2.6 Clinical Examination

- Complete general examination to exclude systemic diseases, inflammatory disorders and malnutrition.
- Complete dermatological examination was done for hair density, hair thickness, facial and body hair distribution and type of AA.
- Measure of the body height and weight to calculate the body mass index

$$\text{BMI} = \text{Mass}_{\text{kg}} \div \text{height}_{\text{m}}^2 \quad (\text{WHO}, 2008).$$
- Clinical details of all patients were recorded.

2.7 Laboratory investigations

All participants were tested for determination of zinc and biotin serum levels.

3. Results

The time of patients bunch extended from 20 years to 55 years (Mean \pm SD = 36.6 \pm 8.019 years), while time of control bunch went from 25 years to 44 years (Mean \pm SD = 33.967 \pm 6.178 years). The weight record (BMI) of patients bunch extended from 19.5 to 27 kg/m² (Mean \pm SD = 23.657 \pm 1.677 kg/m²), while BMI of control bunch went from 22.4 to 26.8 kg/m² (Mean \pm SD = 24.057 \pm 1.106 kg/m²). Thirty patients were male (50 %) and 30 were female (50 %), the benchmark group additionally contain 30 (50 %) male and 30 female (50 %). There was non-huge contrast among patients and control bunches with respect to age (P= 0.298), BMI (P = 0.126) or sex (P = 1.0)

In patients gathering, the length of AA extended from 1 to 15 months (Mean \pm SD = 4.367 \pm 2.917 months),

On clinical assessment the most well-known site were scalp (83.33 %), at that point face (11.67 %), scalp and face (3.33 %) lastly scalp and face and body (1.67 %),

During history taking about past treatment, the outcomes indicated that 34 patients (56.67 %) with no history of past treatment and 26 patients (43.33 %) had a positive history of past treatment

Table (1) Comparison between patients and control groups regarding serum zinc and biotin.

Serum zinc and biotin were estimated in all patients and control gathering. Serum zinc and biotin were lower in patients than in control gathering. In patients gathering, serum zinc level ran from 40 to 91 $\mu\text{g/dl}$ (Mean \pm SD = 60.150 \pm 10.856 $\mu\text{g/dl}$), while in control bunch it ran from 72 to 93 $\mu\text{g/dl}$ (Mean \pm SD = 80.967 \pm 6.407 $\mu\text{g/dl}$). There was a critical distinction as respect serum zinc in patients bunch contrasted with control gathering (P = 0.001)

Serum biotin level in patients bunch ran from 317.8 to 361.2 ng/l (Mean \pm SD = 339.745 \pm 12.031 ng/l), while in control bunch it extended from 436.2 to 531.36 ng/l (Mean \pm SD = 531.360 \pm 33.949 ng/l), and there was a huge contrast between both gathering (P = 0.001)

In male patients, serum zinc level went from 49 to 91 $\mu\text{g/dl}$ (Mean \pm SD = 62.167 \pm 9.931 $\mu\text{g/dl}$), while in male control it ran from 72 to 93 $\mu\text{g/dl}$ (Mean \pm SD = 81.367 \pm 7.233 $\mu\text{g/dl}$). There was a critical distinction as respect serum zinc in male patients contrasted with male control (P = 0.001)

In female patients, serum zinc level went from 40 to 79 $\mu\text{g/dl}$ (Mean \pm SD = 58.133 \pm 11.521 $\mu\text{g/dl}$), while in female control it ran from 74 to 93 $\mu\text{g/dl}$ (Mean \pm SD = 80.567 \pm 5.57 $\mu\text{g/dl}$). There was a critical distinction as respect serum zinc in female patients contrasted with female control (P = 0.001)

In male patients, serum biotin level went from 318.8 to 361.2 ng/l (Mean \pm SD = 342.117 \pm 11.767 ng/l), while in male benchmark group it ran from 536.6 to 583.7 ng/l (Mean \pm SD = 540.313 \pm 8.317 ng/l). There was a critical distinction with respect to serum biotin in male patients contrasted with male control (P = 0.001)

In female patients, serum biotin level went from 317.8 to 354.2 ng/l (Mean \pm SD = 337.373 \pm 12.017 ng/l), while in female benchmark group it ran from 436.2 to 583.7 ng/l (Mean \pm SD = 522.407 \pm 45.932 ng/l). There was a critical distinction with respect to serum biotin in female patients contrasted with female control (P = 0.001)

There was a positive critical relationship between's serum zinc and serum biotin (r = 0.474, P = 0.001)

In understanding gathering, serum zinc demonstrated a non-huge connection with age (r = - 0.222, P = 0.088), BMI (r = - 0.068, P = 0.607), and length of the AA (r = 0.070, P = 0.592)

In understanding gathering, serum biotin demonstrated non-huge connection with age (r = - 0.011, P = 0.933), BMI (r = 0.091, P = 0.491) and length of AA (r = 0.039, P = 0.769)

There were non-critical relations between serum zinc and biotin with sex, history of past treatment and site of the malady

Collector working trademark bend show: Accuracy was 95.1 % for serum zinc and 100 % for serum biotin. Affectability was 86.67 for serum zinc and 100 for serum biotin. Explicitness was 100 in both serum zinc and serum biotin as appeared in Fig (2), Table (3).

		Groups						T-Test	
		Group A			Group B			t	P-value
Serum Zinc (µg/dl)	Range	40	-	91	72	-	93	-12.791	<0.001*
	Mean ±SD	60.150	±	10.856	80.967	±	6.407		
Serum Biotin (ng/l)	Range	317.8	-	361.2	436.2	-	583.7	-41.208	<0.001*
	Mean ±SD	339.745	±	12.031	531.360	±	33.949		

Table (2) Comparison between patients and control groups regarding serum zinc and biotin and sex.

Sex		Serum Zinc (µg/dl)						T-Test	
		Cases			Control			t	P-value
Male	Range	49	-	91	72	-	93	-8.560	<0.001*
	Mean ±SD	62.167	±	9.931	81.367	±	7.233		
Female	Range	40	-	79	74	-	93	-9.606	<0.001*
	Mean ±SD	58.133	±	11.521	80.567	±	5.557		
Serum Biotin (ng/l)									
Male	Range	318.8	-	361.2	536.6	-	583.7	-75.335	<0.001*
	Mean ±SD	342.117	±	11.767	540.313	±	8.317		
Female	Range	317.8	-	354.2	436.2	-	583.7	-21.346	<0.001*
	Mean ±SD	337.373	±	12.017	522.407	±	45.932		

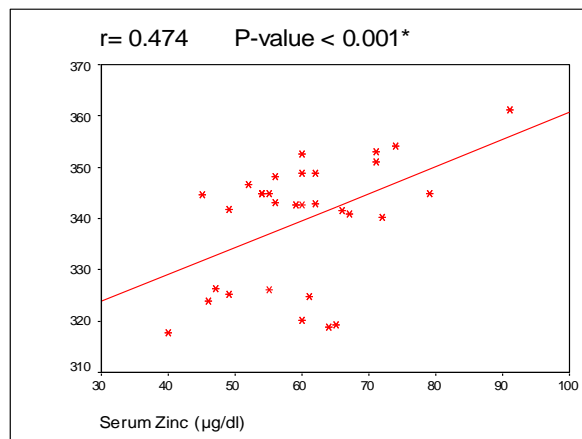


Fig (1) Correlation between serum zinc and biotin.

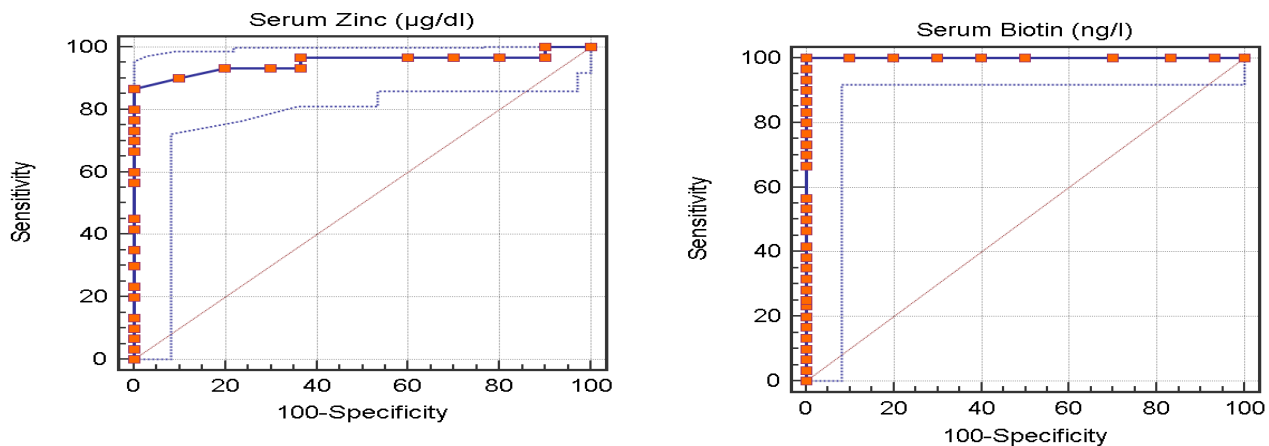


Fig (2) ROC curve between cases and control regarding serum zinc and biotin.

Table (3) ROC curve between cases and control regarding serum zinc and biotin.

	ROC curve between Group A and Group B					
	Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
Serum Zinc ($\mu\text{g/dl}$)	≤ 71	86.67	100.00	100.00	88.2	95.1%
Serum Biotin (ng/l)	≤ 361.2	100.00	100.00	100.00	100.00	100%

4. Discussion

In this investigation, there were non-huge contrast as respect age ($P = 0.298$), BMI ($P = 0.126$) and sex ($P = 1.00$).

In current investigation, serum zinc was altogether lower in patients than in control gathering.

This outcome was steady with Tasaki et al. [7] who detailed equivalent abatements in zinc levels in serum of patients with alopecia areata. Notwithstanding, diminishes in plasma zinc content have been ascribed to decreases in admission or ingestion in small digestive system, or to increments in urinary misfortune, or to redistribution from plasma to tissue. Besides, tissues with high cell turnover (for example skin) are distinctively influenced by zinc inadequacy pointing out the likelihood that some dermatological signs, for example, alopecia areata, might be credited to zinc insufficiency.

This finding is like those of the investigations, where the zinc focus was low in the AA bunches as its worth was 13.8 ± 2.3 [8].

This outcome was predictable with Naginiene et al. [9] found a lower level of zinc in blood and pee of kids with alopecia contrasted with sound people.

It has been accounted for by numerous creators, that AA patients have zinc lack [10]. This upheld the finding of numerous examinations found the serum zinc level diminished in AA patients which empowering the oral zinc sulfate treatment in AA [11].

Additionally, Bhat et al. [12] found that, serum zinc was fundamentally lower in patients than control gathering (Mean \pm SD: 78 ± 7.45 ; 88 ± 8.78 $\mu\text{g/dl}$, separately; $P < 0.05$).

This outcomes was steady with Kil et al. [13] who announced that the serum zinc was altogether lower in AA patients bunch than in charge gathering (Mean \pm SD: 84.96 ± 24.25 ; 97.94 ± 21.05 $\mu\text{g/dl}$, separately; $P = 0.01$).

This outcome was reliable with cross-sectional examination by Shin et al. [14] was carried on 30 sound controls and 312 patients who were determination with alopecia areata. Serum zinc fixations was fundamentally lower in patients examination with control gathering (Mean \pm SD: 84.96 ; 97.94 $\mu\text{g/dl}$, separately; $P = 0.01$).

This outcomes was steady with Abdel Fattah et al. (15) looked at of serum zinc levels between all patients, patients with recently analyzed AA, patients with safe, and controls, the correlation of the various gatherings uncovered a measurably exceptionally critical lower esteems in patients contrasted with controls ($P = 0.001$).

Aiempanakit et al. [16] estimated the plasma zinc levels in patients with AA which were factually fundamentally lower than the control (Mean \pm SD: 61.20 ± 12.00 ; 67.17 ± 10.04 $\mu\text{g/dl}$, individually; $P = 0.04$).

In consistence with our outcomes, proof shows that serum levels of zinc are unquestionably diminished in patients with extreme AA whose alopecia is delayed and is impervious to regular treatments [12]. This suggests the serum levels of zinc are a helpful boundary to anticipate the seriousness and that supplementation of zinc can be a promising adjuvant treatment, alongside standard treatment for extreme AA.

Likewise, like our investigation, among twenty patients were analyzed as having AA was associated with Al-Jaff. [17] study. The mean zinc focus was fundamentally lower in patients contrasted with the benchmark group ($P < 0.001$).

In the current examination, there was a positive critical relationship between's serum zinc and serum biotin ($P = 0.001$).

Correspondingly, zinc insufficiency is accounted for in certain patients with biotin inadequacy [19]. Despite the fact that the serum zinc levels in patients with biotin inadequacy might be gathered as zinc lack may add to the improvement of biotin insufficiency while considering their comparable manifestation profiles yet not fixed outcomes [6].

In current examination, in understanding gathering, serum zinc demonstrated a non-noteworthy connection with age ($P = 0.088$). This outcome was in reliable with Kil et al. [13], who found that there was non-noteworthy connection with age ($P = 0.083$).

Serum zinc likewise demonstrated a non-huge connection with sex ($P = 0.152$), This finding is like those of the examination done by Abdel Fattah et al. [15].

In the current investigation, serum zinc indicated a non-noteworthy relationship with patient's BMI ($P = 0.607$). Ozturk et al. [19] discovered higher serum zinc in patients with high BMI than those with low BMI however the thing that matters was non-noteworthy (Mean \pm SD: 87.77 ± 17.12 , 81.20 ± 16.96 kg/m^2 , individually; $P = 0.13$).

In present examination, serum zinc indicated a non-huge connection with span of the AA ($P = 0.592$). Aiempanakit et al. [16], who found that there was no connection between's zinc levels and the length of AA ($P = 0.31$).

The typical biotin plasma focus ranges from 400 to 1200 ng/L . Insufficiency is actually viewed as a

degree of under 200 ng/L. In any case, plasma biotin levels can change day by day and subsequently are not viewed as a delicate marker [20]. Biotin insufficiency is uncommon, as intestinal microbes are regularly ready to create sufficient degrees of biotin. No clinical preliminaries have indicated viability in treating going bald with biotin supplementation without inadequacy [21]. The biotin advertised enhancements for going bald hand-off on biotin demonstrated beneficial outcomes in the weak fingernails treatment [22].

Supposedly, this is the primary examination that assessed biotin serum levels in AA patients. Aftereffects of current examination uncovered that serum biotin was at the problematic level and essentially lower in patients contrasted with control gathering (Mean \pm SD = 339.745 \pm 12.031; 531.360 \pm 33.949 ng/l separately; P = 0.001). Likewise, in male patients (Mean \pm SD = 342.117 \pm 11.767 ng/l) and in female patients (Mean \pm SD = 337.373 \pm 12.017 ng/l) was altogether lower than in male control (Mean \pm SD = 540.313 \pm 8.317 ng/l) and female control (Mean \pm SD = 522.407 \pm 45.932 ng/l) (P = 0.001 for zinc and biotin).

There are no clinical preliminaries indicating adequacy of biotin on going bald, and it isn't regularly suggested [23]. The utilization of these specialists for balding depends on the perception that alopecia is one of many [24].

Trüeb. [25] estimated the serum biotin level in 503 patients (matured range 9 – 92 years, M = 45.9) grumbling balding. He found that solitary 65 patients had ideal serum biotin level (13 %), 249 patients had imperfect level (49 %), and 189 patients had biotin lack (38%).

Patel et al. [26] dissected 18 case-reports of biotin connection with hair and nail development and discovered clinical improvement in the wake of accepting biotin in all cases, and three revealed instances of uncombable hair disorder demonstrated improvement in hair quality following a couple of long periods of biotin treatment.

Boccaletti et al. [27] contemplated one patient experiencing uncombable hair disorder, and found that the biotin was extremely powerful in the treatment that tolerant. The patient began oral biotin at a measurements of 5 mg/day and following a 3-month time frame they watched noteworthy hair and nail upgrades. At a half year, the patient's hair was thicker and more combable. In addition, after biotin was halted due to worries about medication security, his hair became boisterous once more.

As per Mock. [28] study, hair can be diffusely diminished and fine, however without variations from the norm of the pole in patients with biotin insufficiency.

Innis and Allardyce [29] detailed two instances of going bald in long haul short gut disorder (SBS) patients to without biotin parenteral nourishment. Zinc, copper and lacks of fundamental unsaturated fats

inadequacy were avoided, and going bald was switched with biotin supplementation at 200 mg/day.

Similarly, Khalidi et al. [30] revealed alopecia related with short entrail disorder a half year after initiation of home parenteral sustenance without biotin. New hair development was obvious inside 5 days of biotin supplementation at 60mg/day.

Velazquez et al. [31] created arrangement of patients displayed alopecia, rash, sadness and low plasma biotin levels related with utilization of sans biotin parenteral sustenance for over multi month.

A past report proposed that expanded urinary discharge of 3-hydroxyisovaleric corrosive was a more approved proportion of biotin inadequacy [32]. We prescribe further examinations to assess biotin lack in serum joined with assessment of hydroxyisovaleric corrosive as biotin metabolites in pee o affirm our finding.

In current investigation, in tolerant gathering, serum biotin indicated a non-critical connection with age (r = - 0.011, P = 0.933), BMI (r = 0.091, P = 0.491) and length of AA (r = 0.039, P = 0.769).

So also, El-Esawy et al.(33) found the serum biotin has non-huge relationship with patients' age (r = -0.114, P = 0.387), BMI (r = -0.087, P = 0.508) and sickness term (r = -0.022, P = 0.868).

References

- [1] A.Gilhar, A.Etzioni, R.Paus, Alopecia areata. N. Engl. J. Med, Vol.366, PP.1515–1525. ,2012.
- [2] B.Kamer, W.Wąsowicz, K.Pyziak, Role of selenium and zinc in the pathogenesis of food allergy in infants and young children. Arch. Med. Sci, Vol.8, PP.1083–1088. ,2012.
- [3] C.Hotz, K.H. Brown, ():Assessment of the risk of zinc deficiency in populations and options for its control.Food. And. Nutrition. Bulletin, Vol.25(1 Suppl. 2), S, PP.191–203,2004.
- [4] A.S. Prasad, Zinc and immunity.Mol. Cell. Biochem, Vol.188, PP.63–69
- [5] D.Mock, Skin manifestations of biotin deficiency.Seminars. In. dermatology, Vol.91, PP.296-302, 1991.
- [6] W.Fujimoto, M. Inaoki, T.Fukui, Biotin deficiency in an infant fed with amino acid formula. J.Dermatol, Vol.32, PP.256-261,2005.
- [7] M.Tasaki, K.Hanada, I.Hashimoto, Analyses of serum copper and zinc levels and copper/zinc ratios in skin diseases.The. J., Dermatology, Vol.20, PP.21-24,1993.
- [8] D.Rushton, Nutritional factors and hair loss. Clinical and Experimental Dermatology: Clinical. Dermatology, Vol.27, PP.396-404,2002.
- [9] R.Naginiene, R. Kregzdyte, A.Abdrakhmanovas, Assay of trace elements, thyroid gland and blood indices in children with alopecia. Trace. Elements. And. Electrolytes, Vol.21, PP.207-210,2004.

- [10] P. M. Plonka, B. Handjiski, M. Popik, Zinc as an ambivalent but potent modulator of murine hair growth in vivo—preliminary observations. *Experimental. Dermatology*, Vol.14, PP.844-53,2005.
- [11] L. Dastgheib, Z. Mostafavi-pour, A. A. Abdorazagh, Comparison of zn, cu, and fe content in hair and serum in alopecia areata patients with normal group. *Dermatology. Research. Practice*, Vol.26, PP.255- 262,2014.
- [12] Y. Bhat, S. Manzoor, A. Khan, Trace element levels in alopecia areata. *Indian. J. Dermatol. Venereol. Leprol*, Vol.75, PP.29-31,2009.
- [13] M. Kil, C. Kim, S. Kim, Analysis of serum zinc and copper concentrations in hair loss. *Ann. Dermatol*, Vol.25, PP.405–409,2013.
- [14] S. J. Shin, C. S. Yoo, M. S. Kil, Analysis of serum zinc and copper concentrations in hair loss patients. *프로그램북 (구 초록집)*, Vol.63, PP.140-147,2011.
- [15] N. S. Abdel Fattah, M. M. Atef, S. M. Al-Qaradaghi, Evaluation of serum zinc level in patients with newly diagnosed and resistant alopecia areata. *Int. J. Dermatol*, Vol.55(1), PP.24-29,2016.
- [16] K. Aiempnanakit, K. Chiratikarnwong, T. Chuaprapaisilp, A Study of Plasma Zinc Levels in Thais with Alopecia Areata. *J. Med. Assoc. Thai*, Vol.99, PP.823-7, 2016.
- [17] A. N. Al-Jaff, Role of serum zinc and copper and zinc/copper ratio in alopecia areata. *Iraqi. J., Pharmaceutical. Sciences*, Vol.14, PP.47-51,2017.
- [18] R. Higuchi, M. Mizukoshi, H. Koyama, Intractable diaper dermatitis as an early sign of biotin deficiency. *Acta. Pædiatrica*, Vol.87, PP.228-9,1998.
- [19] P. Ozturk, E. Kurutas, A. Ataseven, BMI and levels of zinc, copper in hair, serum and urine of Turkish male patients with androgenetic alopecia. *J., Trace. Elements. In. Medicine. And. Biology*, Vol.28, PP.266-70,2014.
- [20] J. Zempleni, S. Wijeratne, T. Kuroishi, Biotin. In: Erdman JW, Macdonald IA, Zeisel SH, eds. *Present Knowledge in Nutrition*. 10th ed. Washington, D.C: Wiley-Blackwell, PP.359-74,2012.
- [21] E. L. Guo, R. Katta, Diet and hair loss: effects of nutrient deficiency and supplement use. *Dermatology. Practical. Conceptual*, Vol.7, PP.19-24,2017.
- [22] V. E. Colombo, F. Gerber, M. Bronhofer, G. L. Floersheim, Treatment of brittle fingernails and onychoschizia with biotin: scanning electron microscopy. *J. Am. Acad. Dermatol*, Vol.23, PP.1127-1132,1990.
- [23] N. E. Rogers, M. R. Avram, Medical treatments for male and female pattern hair loss. *Journal of the American Academy of Dermatology*, Vol.59, PP.547-66, 2008.
- [24] J. Zempleni, Y. I. Hassan, S. S. Wijeratne, Biotin and biotinidase deficiency. *Expert. Review. Of. Endocrinology. Metabolism*, Vol.3, PP.715-24,2008.
- [25] R. M. Trüeb, Serum biotin levels in women complaining of hair loss. *International journal of trichology*, Vol.8, 73,2016.
- [26] D. P. Patel, S. M. Swink, L. Castelo-Soccio, A review of the use of biotin for hair loss. *Skin. Appendage. Disorders*, Vol.3, PP.166-9,2017.
- [27] V. Boccaletti, E. Zendri, G. Giordano, L. Gnetti, G. De Panfilis, Familial uncombable hair syndrome: ultrastructural hair study and response to biotin. *Pediatric. Dermatology*, PP.E14–E16,2007.
- [28] D. M. Mock, Skin manifestations of biotin deficiency. *Semin. Dermatol*, Vol.10, PP.296–302,1991.
- [29] S. Innis, D. Allardyce, Possible biotin deficiency in adults receiving long-term total parenteral nutrition. *The. American. J., Clinical. Nutrition*, Vol.37, PP.185-7,1983.
- [30] N. Khalidi, J. R. Wesley, J. G. Thoene, Biotin deficiency in a patient with short bowel syndrome during home parenteral nutrition. *J., Parenteral. And. Enteral nutrition*, Vol.8, PP.311-314,1984.
- [31] A. Velazquez, S. Zamudio, A. Baez, Indicators of biotin status: a study of patients on prolonged total parenteral nutrition. *European. J., Clinical. Nutrition*, Vol.44, PP.11-16,1990.
- [32] J. Zempleni, D. M. Mock, Biotin biochemistry and human requirements. *J. Nutr. Biochem*, Vol.10, PP.128-138,1990.
- [33] F. M. El-Esawy, M. S. Hussein, A. I. Mansour, Serum biotin and zinc in male androgenetic alopecia. *J., Cosmetic. Dermatology*,2019.