Bull. Pharm. Sci., Assiut University, Vol. 46, Issue 2, 2023, pp. 1103-1120.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/
e-mail: bullpharm@aun.edu.eg

DISTURBANCES IN SOME PLASMA AMINO ACIDS METABOLOMIC PROFILES AND THEIR DERIVATIVES IN EGYPTIAN OBESE WOMEN

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Background: *Obesity is a risk factor for several lifestyle diseases such as type II diabetes, hypertension, cancer and others. Studies have shown that plasma amino acids profile may be useful for screening lifestyle diseases. This case-control study aimed at investigating disturbances in acidic, basic, neutral, sulfur-containing amino acids besides imino amino acids profiles in Egyptian obese women to reach a healthy body and to stop any future complications of overweight.* ***Methods:*** *A total of 85 women were enrolled in this study that were classified into 5 groups (17 persons each):1- healthy, 2-overweights, 3-moderate obese, 4-severe obese, 5-morbid obese. Plasma metabolomic profile of the previous amino acids was evaluated using amino acid analyzer.* ***Results:*** *A statistically significant ascending increase in the mean plasma levels of citrulline, glutamate, proline and cysteine together with significant stepwise decrease in ornithine, serine, threonine, aspartate, histidine, arginine, methionine & taurine in obese subgroups as compared to controls.* ***Conclusion:*** *Our results of multivariate regression analysis demonstrated that the significantly elevated circulating lysine or proline levels were the best independent predictors for recognizing obese patients at risk of associated metabolic disorders and that the plasma AA metabolomic profile can be used as important biomarkers for early prediction of overweight women. Amino acids-directed regimens intervention could have significant impact on obesity management.*

Keywords: *Chromatography; Overweight; Obesity-subgroups; Amino acids metabolomic profile; Prediction*

INTRODUCTION

Obesity is a complex disease that affects over one third of the world's populatio[1-4]. Obesity prevalence in Egypt has increased in adults to reach about 40% of its population[5]. Obesity causes annual deaths worldwide due to the associated co-morbidities as type 2 diabetes, hypertension, cardiovascular diseases, hepatic diseases, and cancer.[5]

Previous studies reported that circulating amino acids were useful early-stage diagnostic biomarkers or independent risk factors for prediction of some lifestyle diseases as obesity, diabetes mellitus and heart failure[6-9].

In the present study, we aim to examine the alteration of plasma acidic, basic, hydroxy-containing, sulfur-containing amino acids besides imino-acids profiles in Egyptian obese women in order to reach a healthy body and establish potential preventive strategies for obesity and its future complications.

Received in 6/5/2023 & Accepted in 23/7/2023

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MATERIALS AND METHODS

Patients

The present study is a case control study which is an extension to our previous work[10]. It was conducted in both the Biochemistry Department, Faculty of Medicine, Assiut University & Internal Medicine Department, Assiut University Hospital, Assiut, during the period from August 2021 to August 2022.

A total of 85 Egyptian women that were family unrelated were enrolled in this study. They were selected randomly from the attendants of the out-patients clinic of Internal Medicine Department. The study included 17 age matched, completely healthy control women, with no apparent evidence of any medical disorders. The age of participants ranged between 18-53 years. Their height ranged between 130-185 cm and their weight ranged between 51-135 kg.

The study participants were subdivided into 5 groups according to BMI as follows[11].

- **Group (1):** included 17 healthy controls (normal), with a BMI of 18.5-24.9 kg/m^2.
- **Group (2):** included 17 overweight women, with a BMI of 25-29.9 kg/m^2.
- **Group (3):** included 17 moderate obese women (class I), with a BMI of 30-34.9 kg/m^2.
- **Group (4):** included 17 severe obese women (class II), with a BMI of 35-39.9 kg/m^2.
- **Group (5):** included 17 morbid obese women (class III), with a BMI of ≥40 kg/m^2.

An informed consent was obtained from each patient and control and all study procedures were approved by the Medical Ethics Committee, Faculty of Medicine, Assiut University (IRB no: 17200758). All participants were subjected to full history taking; in addition, detailed clinical and menstrual history was obtained at the time of consent. Personal and relevant data were collected by a questionnaire designed to ask questions about risk factors and co-morbidities of obesity.

All participants were subjected to a thorough clinical examination in the form of complete physical examinations of the chest, heart and abdomen, measurement of blood pressure, body weight, height, waist circumference and hip circumference. Routine laboratory investigations were performed as blood picture, liver functions and kidney functions.

Exclusion criteria included patients with co-morbidities (diabetes, hypertension or insulin resistance (IR), any chronic illness (liver, renal, heart, gastrointestinal, endocrine disorders or thyroid disease), coronary artery diseases, cerebral vascular accidents, active smoking, patients who received any previous treatment for about 6 months later, patients with malignancies and hematologic disorders in addition to lactating and pregnant women.

Obesity indices calculations

1. Body mass index (BMI): was calculated by dividing the weight in kg by square the height in m^2.
2. Body fat percentage (BFP) was calculated according to P. Deurenberg et al., and D. Gallagher et al., [12-13] as follows:
   BFP = (1.2 x BMI) + (0.23 x age in years) – (10.8 x sex) – 5.4, sex is set for zero in women.
3. Fat mass index (FMI): was calculated by dividing the fat mass (FM) in kg by square the height in m^2 where FM = BFP x body weight (Kg) / 100[14-15]
4. 4.Waist circumference/hip circumference ratio (WHR): was calculated.

Sample collection and handling

Four milliliters of antecubital venous fasting blood sample were withdrawn from each patient and control and divided into 3 tubes. Two milliliters of blood were collected in a tube containing heparin for amino acid profile assessment. One milliliter was taken on fluoride for estimation of blood glucose. The rest of the blood were put in a Wassermann test tube, left to clot at room temperature for 10-20 min, then were centrifuged at 3000 rpm for 20 min. Sera were separated and used fresh for estimating the routine laboratory tests and lipid profile.

Lipid profile

Total blood cholesterol, high-density lipoprotein (HDL-C) and triglycerides were assayed using colorimetric kits (catalog

numbers 230006, 266001, 314002), supplied by spectrum diagnostics, Egypt.

Assay of amino acids profile

Assay of amino acids was performed by the ion exchange separation method through high performance liquid chromatography using a Sykam Automatic Amino Acid Analyzer S433 supplied by Sykam GmbH, Germany (catalog no. 1120001). Free amino acid samples were prepared from plasma by acidic protein precipitation, where 200µl of 10% sulfosalicylic acid solution was added to 800 µl plasma, mixed by vortex, then allowed to cool down at about 4 °C for 30 min. it was then centrifuged for 10 min at 14000 rpm. Supernatant liquor was diluted with same amount of sample dilution buffer (catalog no. S000015). One hundred µl of each of prepared samples and ready to use amino acid physiological standard (Catalog no. 6006005) were injected directly. A cation separation column LCAK06/Li was used (catalog no. 5112008) with the following specifications: size: 150 mm× 4.6 mm, specification range: met efficiency: >48000, asymmetry: 0.8–1.5, resolution THR/SER: > 1700, and column pressure: 45–80bar. Buffer: Sykam LiA- 1, LiB-1, LiC-4. The ready to use ninhydrin reagent (catalog no. S000025) and citrate buffers in different pH (2.9, 4.2, and 8.0) were used and the analysis was performed at wavelength 440 nm: 570 nm. The sample chromatogram was compared to the standard measurements curve to obtain various amino acid values, then results were multiplied by a dilution factor of 2.5.

Statistical analysis

The entry and data analysis were done using IBM-SPSS version 26 (Statistical Package for Social Science) for windows software. Continuous data were expressed as number, mean ± standard deviation (Mean ± SD) or median and Interquartile range (Median (IQ)). The normal distribution of the data was determined using the Shapiro-Wilk test. Statistical comparison of differences between test groups was evaluated by one-way ANOVA for parametric data, or Kruskal Wallis test for non-parametric data. The correlation coefficients analysis was performed using Pearson's coefficients. Univariate and multivariate regression analysis were performed to assess the effect of individual amino acids as independent risk factors for obesity. A two-tailed P-value was considered statistically significant when $P < 0.05$.

RESULTS AND DISCUSSION

Results

Anthropometric data of subjects

The anthropometric data in the four subgroups of patients (overweight and obese classes I, II & III) are shown in **Table 1** compared to controls (group 1). There was no statistical significance regarding age between the five groups. There were stepwise increases in weight, waist and hip circumferences of obese women when compared to the controls.

Obesity indices

This present study presents the levels of BMI, waist/hip ratio (WHR), fat mass index (FMI) and body fat percent (BFP) among obese subgroups and controls. Highly significant differences were found between controls and other obese subgroups regarding all parameters and the morbid obese group exhibited the highest values. **Table 2**

Biochemical investigations

This present data shows the mean levels of glucose where no significant differences were detected between any of the groups. In addition, Hb. and kidney function levels were normal in all groups (data not shown). As for liver function tests, despite their normal reference ranges, some differences were observed between controls and other obese subgroups. Also, the mean values of serum total cholesterol, LDL-C and triglycerides levels were significantly higher with HDL-C significantly lower in obese women than that of controls. **(Table3)**

Table 1: Anthropometric data of different study groups .

	Controls (n=17)	**Overweight (n=17)**	**Moderate Obese (n=17)**	**Severe Obese (n=17)**	**Morbid Obese (n=17)**
Age (Year)					
Mean±SD	31.41±8.11	34.71±6.3	31.41±7.92	33±9.63	37.76±8.07
P1		NS	NS	NS	NS
P2			NS	NS	NS
P3				NS	NS
P4					NS
Weight (Kg)					
Mean±SD	69.24±12.79	79.06±8.71	81.94±14.45	92.35±10.39	105.71±17.35
P1		NS	NS	<0.001	<0.001
P2			NS	<0.001	<0.001
P3				<0.01	<0.001
P4					<0.05
Height (Cm)					
Mean±SD	170.41±13.09	165.82±9.17	156.59±8.85	156.35±8.43	151.06±10.19
P1		NS	<0.01	<0.01	<0.001
P2			<0.01	<0.01	<0.001
P3				NS	NS
P4					NS
Waist Circum.(Cm)					
Mean±SD	84.82±5.58	101.82±11.48	101.76±11.12	112.76±16.1	130.41±13.99
P1		<0.001	<0.001	<0.001	<0.001
P2			NS	<0.05	<0.001
P3				<0.05	<0.001
P4					<0.01
Hip Circum.(Cm)					
Mean±SD	109.88±8.26	123.65±14.14	121.88±10.4	129.59±16.92	143.82±14.31
P1		<0.01	<0.01	<0.001	<0.001
P2			NS	NS	<0.001
P3				NS	<0.001
P4					<0.05

P1: comparison between control & other groups.
P2: comparison between overweight & other groups.
P3: comparison between moderate obese & other groups.
P4: comparison between severe obese & morbid obese.

Table 2: Obesity indices among different study groups.

	Controls (n=17)	**Overweight (n=17)**	**Moderate Obese (n=17)**	**Severe Obese (n=17)**	**Morbid Obese (n=17)**
BMI (Kg/m²)					
Mean±SD	23.56±1.44	28.48±1.32	33.32±5	37.72±1.75	46.08±4.74
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
WHR(W/H)					
Mean±SD	0.77±0.03	0.82±0.02	0.83±0.02	0.86±0.02	0.9±0.04
P1		<0.001	<0.001	<0.001	<0.001
P2			NS	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.01
BFP(BF%)					
Mean±SD	30.09±3.19	36.76±2.16	41.81±6.78	48.89±2.09	58.58±5.09
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
FMI (kg/m²)					
Mean±SD	7.14±1.16	10.58±1.1	14.26±5.38	18.82±1.23	27.25±5.57
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001

P1: comparison between control & other groups.
P2: comparison between overweight & other groups.
P3: comparison between moderate obese & other groups.
P4: comparison between severe obese & morbid obese.

Table 3: Biochemical data of different study groups.

	Controls (n=17)	Overweight (n=17)	Moderate Obese (n=17)	Severe Obese (n=17)	Morbid Obese (n=17)
Glucose (mmol/L)					
Mean±SD	5.37±0.87	5.49±1.08	5.08±0.9	5.31±1.11	5.6±1.17
P1		NS	NS	NS	NS
P2			NS	NS	NS
P3				NS	NS
P4					NS
AST (IU/L)					
Mean±SD	12.59±2.24	15.29±1.76	14.94±1.25	12.94±1.71	14.53±1.12
P1		<0.01	<0.01	NS	<0.01
P2			NS	<0.001	NS
P3				<0.001	NS
P4					<0.01
ALT (IU/L)					
Mean±SD	8.53±2.12	18.47±1.81	14.06±0.83	23.53±3.02	21.88±2.39
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					NS
ALP (IU/L)					
Mean±SD	61.71±5.67	44.59±3.83	64.18±2.92	64.35±4.11	82.24±2.97
P1		<0.001	NS	NS	<0.001
P2			<0.001	<0.001	<0.001
P3				NS	<0.001
P4					<0.001
Serum Cholesterol (mg/dl)					
Range	124.61 - 170	121.29 - 182	156 - 199.33	160 - 213.33	186.66 - 273.33
Mean±SD	145.31±16.64	157.01±16.76	176.9±16.23	182.35±15.62	227.05±23.98
P1		NS	<0.001	<0.001	<0.001
P2			<0.01	<0.001	<0.001
P3				NS	<0.001
P4					<0.001
HDL-C (mg/dl)					
Range	47.88 - 55.86	37.62 - 49.02	27.36 - 38.76	25.08 - 29.64	18.24 - 31.92
Mean±SD	52.44±2.74	42.11±3.11	33.26±3.76	27.76±1.66	24.21±5.01
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.05
LDL-C (mg/dl)					
Range	56.49 - 97.42	60.67 - 108.01	89.66 - 135.3	90.5 - 150.11	127.14 - 207.67
Mean±SD	75.23±15.14	90.96±14.43	112.87±16.86	115.65±16.86	159.08±24.82
P1		<0.05	<0.001	<0.001	<0.001
P2			<0.01	<0.001	<0.001
P3				NS	<0.001
P4					<0.001
Serum TAG (mg/dl)					
Range	70 - 100	105 - 135	140 - 170	185 - 210	190 - 235
Mean±SD	88.24±8.83	119.71±9.6	153.82±9.93	194.71±8.19	218.82±11.53
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001

P1: comparison between control & other groups. **P2**: comparison between overweight & other groups.
P3: comparison between moderate obese & other groups. **P4**: comparison between severe obese & morbid obese.

Plasma concentrations of amino acids in different study groups

The next tables present the comparison between overweight, obese subgroups and controls regarding the plasma metabolomics profile of AAs. Overweight and obese subgroups exhibited significantly lower levels of nine AAs (serine, threonine, aspartate, aspargine, histidine, arginine, methionine, ornithine and taurine) when compared to controls. In addition, higher levels of 5 AAs (glutamate, phosphoserine, cysteine, proline and citrulline were found in overweight and obese subgroups versus controls. Moreover, significant changes were observed among overweight and obese subgroups and among each of subgroups.

Plasma concentrations of acidic amino acids

A significant decrease was observed in the plasma aspartic levels in all subgroups as compared to that of controls. The mean levels were significantly decreased in a descending order in the three obese subgroups. Meanwhile, there was no significant difference in aspartate levels between overweight and moderate obese groups **(Table 4).** As for glutamic acid, the mean plasma levels were found to increase significantly in a rising titer in obese subgroups **(Table 5)**.

Plasma concentrations of basic amino acids

Histidine and arginine were significantly decreased in a descending manner in all subgroups as compared of that of controls. The decrease in lysine was not significant, except in the severe obese group. In contrast, the lysine levels in the morbid group were significantly increased in comparison to that of controls **(Table 4)**.

Plasma concentrations of hydroxy-containing amino acids

The mean plasma levels of serine and threonine amino acids were significantly decreased in a descending manner in all subgroups as compared to that of controls. There was a significant change between groups **(Table 4)**. In contrast, phosphoserine mean levels were found to be significantly increased in all groups as compared to that of the controls and in relation to each other except for the moderate obese group which exhibited the same level as the overweight group **(Table 5)**.

Plasma concentrations of the sulphur containing amino acids

The mean plasma level of cysteine was significantly increased, in all obese subgroups as compared to that of the controls and in relation to each other; however, differences were not significant between severe and moderate or between severe and morbid obese group **(Table 5)**. On the other hand, methionine level was significantly decreased in all obese subgroups as compared to that of the controls **(Table 4)**.

Plasma concentrations of amine and imino amino acids

The mean plasma level of asparagine amino acid was decreased in all obese subgroups in a descending order as compared to that of controls and in relation to each other **(Table 4)**. Whereas, the mean plasma level of proline was found to be increased in all obese subgroups as compared to that of controls **(Table 5)**.

Plasma concentrations of amino acids-derivatives

There was a significant stepwise decrease in each of taurine and ornithine in all groups as compared to that of controls, as well as in between all groups **(Table 4)**. Concerning citrulline, it was significantly elevated in a stepwise fashion in its plasma level in obese subgroups **(Table 5)**.

Dependent Variable: BMI (Kg/m^2)

The above table shows the univariate and multivariate regression analysis of the studied amino acids for evaluation of the independent risk factors for obesity cases. The left side of the table shows the univariate regression analysis to assess the effect of individual amino acids. Analysis revealed that all amino acids are significant independent risk factors for obesity except cysteine. At the right side, multivariate analysis is presented where odds ratio is adjusted to BMI. The study demonstrated that only lysine and proline are significant independent risk factors for obesity cases (<0.02 each). **(Table 6**).

Table 4: Profiles of the amino acids that were reduced in overweight and obese groups compared to controls**.**

(µmol/L)	Controls (n=17)	Over Weight (n=17)	Moderate Obese (n=17)	Severe Obese (n=17)	Morbid Obese (n=17)
Serine	166.88±25.46	101.9±3.61	96.79±1.81	81.33±1.81	70.73±2.03
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
Threonine	162.85±31.3	103.87±2.98	94.8±0.96	85.08±4.35	56.24±9.68
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
Aspartic acid	15.22±1.74	6.53±0	6.53±0	3.73±0.42	2.71±1.11
P1		<0.001	<0.001	<0.001	<0.001
P2			NS	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
Histidine	83.47±9.28	65.85±2.58	56.55±2.03	45.36±0.61	37.3±1.86
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
Arginine	153.2±92.51	71.72±5.67	62.18±0.28	57.04±1.74	40.11±4.73
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
Methionine	82.11±11.8	67.93±0.17	55.68±1.67	42.41±0.51	44.71±1.28
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
Aspargine	86.5±28.31	73.57±8.95	65.36±3.74	54.91±2.08	41.09±9.48
P1		NS	NS	<0.001	<0.001
P2			NS	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
Lysine	151.61±26	100.26±9.35	124.05±3.3	138.83±10.04	174.94±5.81
P1		<0.001	<0.01	NS	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001
Ornithine	178.18±57.01	92.54±3.66	76.44±1.71	49.98±1.87	42.63±4.98
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001

Table 1: Continued.

Taurine	293.19±79.01	69.15±6.16	48.8±4.27	38.29±0.64	27.37±2.33
P1		<0.001	<0.001	<0.001	<0.001
P2			<0.001	<0.001	<0.001
P3				<0.001	<0.001
P4					<0.001

P1: comparison between control & other groups. **P2**: comparison between overweight & other groups. **P3**: comparison between moderate obese & other groups. **P4**: comparison between severe obese & morbid obese.

Table 5: Profiles of the amino acids that were increased in overweight and obese groups compared to controls.

(µmol/L)	**Controls (n=17)**	**Overweight (n=17)**	**Moderate Obese (n=17)**	**Severe Obese (n=17)**	**Morbid Obese (n=17)**
Glutamic acid	47.73±10.86	65.87±1.53	53.22±2.2	75.24±2.85	111.1±18.98
		<0.001	NS	<0.001	<0.001
			<0.001	<0.001	<0.001
				<0.001	<0.001
					<0.001
Phospho-serine	9.02±1.42	12.08±0.31	12.08±0.31	13.57±0.34	18.63±0.8
		<0.001	<0.001	<0.001	<0.001
			NS	<0.001	<0.001
				<0.001	<0.001
					<0.001
Cysteine	10.29±2.71	26.48±20.9	27.06±3.78	42.39±22.86	29.94±1.96
		<0.001	<0.001	<0.001	<0.001
			<0.001	<0.001	<0.001
				NS	<0.001
					NS
Proline	175.61±16.5	285.36±106.6	399.64±56.68	225.51±14.8	431.13±40.01
		<0.001	<0.001	<0.001	<0.001
			<0.01	NS	<0.001
				<0.001	NS
					<0.001
Citrulline	14.37±5.75	77.02±2.11	67.36±1.6	138.16±16.71	105.8±2.46
		<0.001	<0.001	<0.001	<0.001
			<0.001	<0.001	<0.001
				<0.001	<0.001
					<0.001

P1: comparison between control & other groups. **P2**: comparison between overweight & other groups. **P3**: comparison between moderate obese & other groups. **P4**: comparison between severe obese & morbid obese.

Table 6: Univariate & Multivariate regression analysis of the studied amino acids (µmol/L) as independent risk factors for obesity cases.

	Univariate				Multivariate			
	OR	95.0% CI		P. value	OR	95.0% CI		P. value
		Lower	Upper			Lower	Upper	
Citrulline	0.701	0.109	0.171	0.000	-	-	-	-
Ornithine	-0.723	-0.134	-0.088	0.000	-	-	-	-
Serine	-0.754	-0.212	-0.144	0.000	-	-	-	-
Phospho-serine	0.865	1.957	2.524	0.000	-	-	-	-
Threonine	-0.799	-0.206	-0.148	0.000	-	-	-	-
Glutamate	0.752	0.209	0.308	0.000	-	-	-	-
Aspartic acid	-0.784	-1.711	-1.207	0.000	-	-	-	-
Aspargine	-0.684	-0.342	-0.213	0.000	-	-	-	-
Histidine	-0.852	-0.485	-0.370	0.000	-	-	-	-
Arginine	-0.529	-0.106	-0.051	0.000	-	-	-	-
Lysine	**0.451**	**0.076**	**0.191**	**0.000**	**0.532**	**0.027**	**0.287**	**0.018**
Methionine	-0.790	-0.492	-0.349	0.000	-	-	-	-
Cysteine	-0.127	-0.054	0.014	0.245	-	-	-	-
Taurine	-0.666	-0.066	-0.040	0.000	-	-	-	-
Proline	**0.583**	**0.030**	**0.056**	**0.000**	**0.320**	**0.005**	**0.043**	**0.016**
AA	0.318	0.002	0.011	0.003	-	-	-	-

Discussion

Obesity is a global pandemic of the present century [16-18]. It is a risk factor for several diseases such as type 2 diabetes, hypertension, cardiovascular diseases, hepatic diseases, and cancer [19]. This can lead to a reduced life quality and increases the overall risk of morbidity and mortality [20]. Hence, it is of utmost importance to assess risk factors that help in early detection and management of obesity.

Several reports demonstrated that altered plasma amino acids profiles are associated with harmful metabolic disorders like obesity[21-23].

The mean plasma levels of glutamate were found to increase significantly in a rising titre in all obese subgroups as compared to the controls except in the moderate obese group that was not significant.

Glutamate showed positive correlations with each of BMI, WHR & FMI which are in accordance with the results of Gaggini M.; Yu HT. et al.; Wang VH. et al. and Short, KR. et al.[24-27] who suggested that this correlation may be related to the regulation of food intake and insulin levels.

On the other hand, aspartate and asparagine levels in our study revealed significantly decreased levels in all obese subgroups, in a descending manner, as compared to controls with highly significant negative correlations with each of obesity indices. These decreased levels may be due to liver steatosis that might found in class III obese group. There are no previous reports discussing aspartate levels in obesity.

Some evidence suggests that, altered populations of gut microbiota that metabolize glutamate and glutamine may contribute to the changes in the plasma concentrations of these AAs[28].

Glutathione (GSH), one of the most abundant antioxidants in animals, is synthesized intracellularly from L-glutamic acid, L-cysteine, and glycine by the enzymes γ-glutamylcysteine synthetase and GSH synthetase. Notably, GSH in the body is usually provided by oral administration of GSH precursors (such as glycine and L-cysteine)

rather than GSH itself since oral GSH administration is inefficient in improving its content[29]**.** Increasing the GSH content via supplementation of glycine alone or together with cysteine provides protective effects against the disorders of lipid metabolism.

It is well-recognized that reactive oxygen species (ROS) and oxidative stress play critical roles in the development of insulin resistance, hypertension, and obesity[30]. Recent evidence implicates reduced ROS and oxidative stress across the role of GSH biogenesis in the prevention and treatment of obesity and its related metabolic disorders.

Another potential mechanism by which GSH could combat obesity-related metabolic diseases is via improvements in mitochondrial fat and carbohydrates oxidation[31].

α-Ketoglutarate is a weak acid that can be produced during glutamine metabolism **[32].** An increasing body of literature identifies α-Ketoglutarate as a potential nutritional tool to prevent and combat obesity and its related metabolic disorders[33].

In the current study, the mean plasma levels of histidine and arginine were significantly decreased in a stepwise manner in all obese subgroups. This finding is consistent with the results of Tang JE et al. and Sailer M. et al. **[34- 35].** As for lysine levels, they were significantly decreased in subgroups except in severe obese group, it was non-significant. In contrast, it is significantly increased in class III obese group in comparison to those of controls. These findings confirmed the previous results of Niu YC et al.[36].

On the other hand, histidine, arginine and ornithine mean levels were found to be significantly negatively correlated with obesity indices, whereas, lysine levels showed significant positive correlations with those indices. These data are in accordance with those of Li, YC. et al.[37]**.**

Lysine proved, in the present study, (by multivariate analysis) to be one of the best independent predictors or risk factors for recognizing obese patients at risk for associated metabolic disorders development.

Arginine is classified in adults as non-essential as its endogenous synthesis from citrulline is enough. In acute events or inflammatory conditions, endogenous Arg synthesis will be not enough, making it essential[38- 39]. This may represent the minimal degree of inflammatory state in our obese subgroups.

Arginine is a precursor for ornithine, nitric oxide (NO), polyamines and many other biologically important molecules. Therefore, the decrease of body Arginine level will subsequently lead to a decrease of ornithine. Arginase is an enzyme of urea cycle that hydrolyzes L- arginine to urea and L- ornithine. Then, ornithine is converted to citrulline, in turn citrulline is converted endogenously to arginine[40]**.** Moreover, NO and citrulline can be synthesized from arginine by NO- synthase[41]**.** Therefore a cyclic relation exists between the three AA[39].

The plasma concentrations of citrulline, in the present study, showed a significant increase in all obesity subgroups with signficant positive correlations with obesity indices. This finding is in line with She P. et al. and Sailer M. et al. **[42, 35]** who proposed an alteration in urea cycle synthesis in liver of obese persons i.e. block in cytosolic reactions due to liver steatosis. This may be the cause for ornithine and citrulline plasma levels change in our obese subgroups. Maya, K et al.**[43]** suggested that L-citrulline supplementation has effects on hypertension and oxidant stress. It improves metabolic syndrome through decreased body weight by appetite suppression. In contrast**,** Newgard CB. et al. and Park S. et al. [44- 45] found unaltered serum citrulline in obese subjects and diabetic patients.

Histidine is a semi-essential AA in adults (essential in children), it can be condensed with β–alanine to form carnosine and anserine which are involved in protection against oxidative stress[46]. It can also be converted via decarboxylation into histamine which act as a neurotransmitter or it can be irreversibly degraded to urocanic acid & ammonia[46] by histidase enzyme. Previous reports suggested that, the use of antihistaminics and antipsychotic drugs (H1 blockers) are associated with increased risk for obesity[47]**.** In rats, the highest concentration of brain histamine is found in hypothalamus by activating its receptor, an increase in hypothalamic histamine concentration, suppresses food intake, accelerates lipolysis and upregulates UCP proteins in adipose tissue.

The study suggested that, histamine is an essential regulator of energy homeostasis [48].

Our results which mentionned before confirming the recent suggestions that, supplementation with dietary histidine might improve inflammation and energy homeostasis in overweight and obese people[49].

The data of Libert DM et al.,[8] revealed that lysine increased with metabolic unwellness and had nearly significant increases in obese and diabetic states. Moreover, lysine[50] and histidine[51] supplementation suppresses food intake, impact thermogenesis and lipid metabolism. The reduction of body weight and food intake by lysine may be due to the uptake competency between both AAs and the resulting reduced NO production after supplementation where they share the same transport system [52].

One explanation for the elevation in plasma lysine is its mobilization to provide alpha-aminoadipic acid, the product of lysine degradation, to promote insulin secretion and maintain glucose homeostasis in early insulin resistance[53]. This may represent the status of the present study morbid obese group.

In the current study, obese women were associated with significantly lower levels of Serine. This is in accordance with the results of Takashina et al., Gaggini, M., Simmons, RM, et al.[54, 24,55]. Serine is synthesized from glycolytic intermediates via 3-phosphoglycerate dehydrogenase, the rate limiting step of de novo serine biosynthesis[56]. Serine can be also synthesized in the liver by phosphoenol pyruvate carboxykinase in gluconeogenesis. Thus, the changes in glyceroneogenesis in adipose tissue and liver due to increased glycerol demand for triacylglycerols synthesis may affect serine biosynthesis and its subsequent level in circulation[57]. This could explain the present study serine lower levels associated with obesity.

The phosphorylation of specific serine residues of proteins can regulate the activity of certain enzymes of lipid and carbohydrate metabolism[58]. So, in the current study, the increased phosphoserine levels may be a trial to regulate the obese patients metabolic pathways.

Threonine plasma levels showed a significant stepwise decline in all obese subgroups compared to controls. It showed a highly significant negative correlation with obesity indices. These findings are in consistence with those of previous authors [37]. The decrease in threonine levels in our study may be due to its decreased intake as it is an essential AA.

Methionine is an essential amino acid and is involved in several metabolic processes such as the synthesis of carnitine that is essential for fatty acid oxidation[59]. Methionine is also an essential antioxidant as it can detoxify free radicals by its sulfur group[60]. Upon activation, methionine is converted to s-adenosyl methionine which acts as a methyl donor **[61].** Methionine after its demethylation is converted to homocysteine that is catabolized to cystathionine and subsequently to cysteine[62]. Cysteine is a precursor of the antioxidant glutathione, and taurine via catabolism by enzyme cysteine-dioxygenase [20].

Previous epidemiologic and animal studies suggested that cysteine is obesogenic[63]**.** Cysteine can inhibit lipolysis and promotes lipogenesis in adipocytes via H_2O_2 production. In vitro, H_2O_2 stimulates enzymes and pathways that favour lipid storage and driving metabolic complications of obesity[64]**.** A positive relationship was reported between cysteine and BMI in overweight individuals **[65].** Plasma cystine is also strongly associated with BMI[66]**.** Experimental and epidemiologic evidence suggests that cysteine could be an unrecognized determinant of body weight[63].

Moreover, Methionine and cysteine synthesize taurine. Low taurine in those patients could be produced by the deficiency of Methionine precursor along with inflammation and oxidative damage associated with obesity[30, 67]. Taurine, one of the most abundant AAs in animals is obtained via two pathways: one is the exogenous pathway where taurine is provided by diets and the other is the endogenous pathway by de novo synthesis[68]**.** Taurine can exert important physiological effects, upon supplementation, such as the modulation of lipid metabolism. An increasing body of literature identifies taurine supplementation as a potential regulator in the prevention and/or treatment of obesity and its related metabolic diseases[67].

Taurine might counteract obesity via regulating the polarization of macrophages toward an anti-inflammatory M2 phenotype to

mitigate chronic inflammation in adipose tissues, which has been recognized as a causative factor for the development of obesity and its related metabolic diseases[69].

The mean plasma levels of proline in our study were found to be increased gradually in all obese subgroups as compared to that of controls. The significantly highest levels of proline were exhibited by the morbid (class III) obese group. The study demonstrated also, significant positive correlations between proline and obesity indices (BMI, WHR and FMI).These findings are consistent with the previous reports[70, 7] where increased proline levels were found in obese patients. The increased proline in our obese women may be attributed to the increased glutamate as it can be formed from glutamate through glutamate semialdehyde. Furthermore, we demonstrated that proline and lysine are independent risk factors for obesity cases that remained significant after adjustment for BMI in multivariate regression analysis suggesting the direct pathophysiological relationship between these AA and obesity implications.

These significantly high circulating levels of proline and lysine were the best independent predictors for recognizing obese patients at increased risk for developing associated metabolic disorders as poor glycemic control, hypertension, liver steatosis or insulin resistance. Proline relationship to obesity has scarcely been studied by the previous authors.

In conclusion

The present study revealed that, plasma AA- metabolomic profile could provide an accurate measure for obesity severity or its elevated indices and give essential informations to elaborate sub-classifications within obese patients. This can lead to accurately predict and prevent the development of obesity and its severe complications during its progression.

The multivariate regression analysis adjusted to BMI, performed in the current study showed that, the significantly elevated lysine and proline plasma levels were the best independent predictors for identifying obese patients at risk of associated metabolic disorders or pathophysiology.

Recommendations

1. Finding effective preventive approaches to reduce the obesity prevalence & enhance quality of life is a major challenge. The noninvasive lifestyle modification e.g. nutrients-balanced diet containing high biological value proteins, intermittent fasting or aerobic exercise training could be effective in weight loss for overweight or early obese women.
2. AA-directed regimens interventions, aimed at dietary supplementation or restrictions of specific AA, could treat or even prevent the development of obesity & slow its future metabolic complications. This can be done, provided that; the AA has no side effects and must be carefully adjusted in concentration by monitoring its free level.

Limitations

A wide scale study with a larger sample size is needed to extend these results and to shed more light on plasma AA metabolomic profile and on other different metabolomics implications in obese persons.

Ethics approval

All study procedures were approved by the Medical Ethics Committee, Faculty of Medicine, Assiut University (IRB no: 17200758).

Consent for publication

Participants have consented to the submission of data.

Acknowledgments

The authors acknowledge the technical help of Metabolic and Genetic disorders Unit, Assiut University.

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Bull. Pharm. Sci., Assiut University, Vol. 46, Issue 2, 2023, pp. 1103-1120.

نشرة العلوم الصيدلية
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

الاضطرابات في بعض الملامح الأيضية للأحماض الأمينية ومشتقاتها في البلازما في السيدات المصريات البدينات

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تعد السمنة عاملا مؤثرا في العديد من أمراض نمط الحياة مثل النوع الثاني من مرض السكري وارتفاع ضغط الدم وغيرها. أظهرت الدراسات أن نمط الأحماض الأمينية في البلازما قد يكون مفيد في فحص العديد من أمراض نمط الحياة.

تهدف هذه الدراسة إلى البحث في اضطرابات الأحماض الأمينية الحامضية والقاعدية والمتعادلة والمحتوية على الكبريت بالإضافة إلى الأحماض الأمينية المحتوية على مجموعة الإمينو في السيدات المصريات البدينات.

تم تسجيل ٨٥ امرأة في هذه الدراسة وتم تصنيفهن إلى ٥ مجموعات (١٧ فردًا لكل مجموعة):

١- أصحاء ، ٢- وزن زائد ، ٣- متوسطي السمنة ، ٤- سمنة شديدة ، ٥- سمنة مفرطة.

تم تقييم النمط الأيضي للبلازما للأحماض الأمينية السابق ذكرها باستخدام جهاز تحليل الأحماض الأمينية.

أظهرت نتائج الدراسة زيادة تصاعدية ذات دلالة إحصائية في متوسط مستويات البلازما من السيترولين والجلوتامات والبرولين والسيستين مع انخفاض تدريجي معنوي في الأورنيثين والسيرين و الثريونين والأسبارتات و الهيستيدين و الأرجينين و الميثيونين والتورين في مجموعات السمنة الفرعية مقارنة بالمجموعة الضابطة.

وخلصت الدراسة الى أن نتائج تحليل الانحدار متعدد المتغيرات من مستويات اللايسين أو البرولين المرتفعة بشكل ملحوظ كانت أفضل مؤشرات مستقلة للتعرف على المرضى الذين يعانون من السمنة المفرطة المعرضين لخطر الاضطرابات الأيضية المصاحبة.