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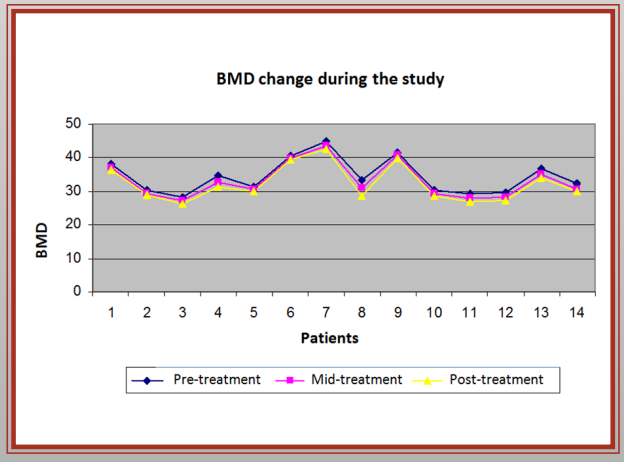

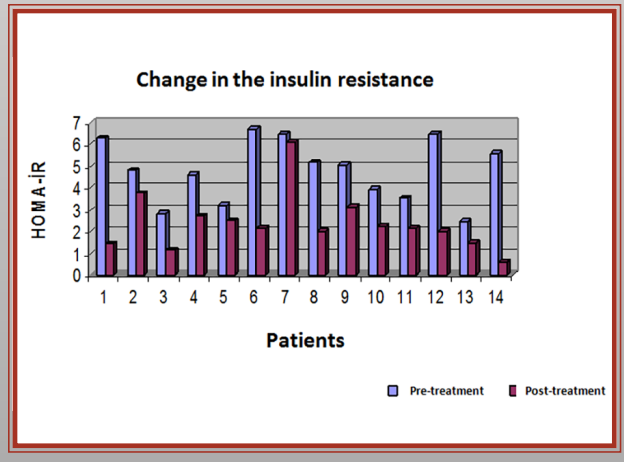

galenos yayinevi

INHERITED METABOLIC DISORDERS AND NUTRITION

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INHERITED METABOLIC DISORDERS AND NUTRITION

Editorial

Dear Colleagues,

We are delighted to announce the launch of the inaugural issue of Inherited Metabolic Disorders and Nutrition (IMDN), the official journal of the Child Nutrition and Metabolism Association. The journal provides a platform for academics to advance scientific research, report rare case studies, and share innovative ideas - all contributing to the growing body of knowledge in our field.

Inherited metabolic disorders represent a critical area of research, with an increasing number of researchers and publications dedicated to this field worldwide. IMDN was established in response to the ongoing need for additional avenues to publish high-quality research in this area. The journal aspires to make a lasting contribution to the fields of paediatric nutrition and inherited metabolic disorders. With the release of the first issue, a strong commitment is renewed to position IMDN as a leading resource within the international scientific community. Over time, we hope that IMDN will become an essential tool for sharing information and experiences related to metabolic disorders and nutrition.

IMDN will be published quarterly and will feature peer-reviewed research articles, case reports, reviews, original studies, and other relevant content. Our editorial board comprises experts from around the globe, and we welcome contributions from our international colleagues.

For more information about IMDN, please visit our website at www.imdn.org. I encourage you to read the first issue with great interest, and I extend my sincere thanks to the authors whose work is featured in it. As a newly established journal, IMDN will undoubtedly thrive with your continued support and contributions.

We look forward to receiving your submissions for future issues.

Best regards,
Nur Arslan
Editor-in-Chief, Inherited Metabolic Disorders and Nutrition (IMDN)

INHERITED METABOLIC DISORDERS AND NUTRITION

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ORIGINAL ARTICLE

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Inherit Metab Disord Nutr 2025;1(1):1-8

Use of Acti-Heart® in Diagnosis, Follow-Up, and Evaluation of Obesity in Childhood and its Relationship to Other Metabolic Parameters

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Abstract

Objectives: In this study we evaluated changes in lifestyle and motivation, obesity diagnosis, diet and exercise treatments in adolescents using Acti-Heart®, as well as effects on body composition, lipid profile, insulin resistance (IR), adipocytokines, basal metabolic rate and daily calorie consumption.

Materials and Methods: A total of 14 cases with an age range of 10.1-16.6 years, and puberty stage of III-IV, who were followed up in our department with a diagnosis of exogenous obesity were included. Thirteen children were included as the control group. Body mass index (BMI), waist and hip circumferences, waist/hip ratio, body fat percentage, skin fold thickness measurements were performed, and glucose, insulin, homeostasis model assessment of IR (HOMA-IR), total cholesterol, low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), triglyceride, serum aspartate and alanin aminotransferase (AST and ALT), visfatin, tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10) and apolipoprotein A (APO A) levels were determined. Calorie consumption was measured using Acti-Heart®.

Results: In our patient group, BMI, ALT, glucose, insulin, HOMA-IR, total cholesterol, LDL-C, VLDL-C, triglyceride, visfatin values were high, but TNF-α, IL-10 and APO A levels were low ($p<0.05$). BMI, waist and hip circumferences, waist/hip ratio, body fat percentage and skin fold thickness decreased in with diet, exercise, and behavioral therapy. HOMA-IR, AST, ALT, VLDL-C, triglyceride, visfatin and hs-C-reactive protein values were also decreased. However, TNF-α, IL-6, and IL-10 levels increased. Daily calorie consumptions measured by Acti-Heart® significantly increased ($p=0.004$).

Conclusion: This is important as it shows increased calorie consumption, parallel changes in body composition, and improvements in metabolic parameters such as decreased VLDL, triglyceride, and IR using Acti-Heart® in obesity treatment monitoring in adolescents. In conclusion, Acti-Heart® is an objective evaluation method for monitoring obesity treatment. The study is planned to be conducted in larger groups of obese children.

Keywords: Body Mass Index, Diet, Insulin Resistance, Lipids, Obesity, Visfatin

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INTRODUCTION

Obesity is a complex, multifactorial disease caused by an imbalance in calorie intake and energy expenditure. The most important cause of obesity is the intake of more energy than consumed. Childhood obesity refers to an unhealthy excess of body fat.[1] The world-wide increase in obesity, which can adversely affect the health of children, appears to be largely influenced by environmental factors, lifestyle and cultural aspects.[2] Childhood obesity has emerged as a global health problem due to its increasing prevalence in both developed and developing countries.[3] Currently, approximately 170 million children worldwide are overweight or obese.[3,4]

Childhood obesity serves as a major contributing factor to the development of several diet-related chronic conditions, including later life conditions such as heart disease, high blood pressure, stroke, type II diabetes, and several types of cancer.[5] Various treatment methods such as appropriate diet preparation, increased physical activity, behavioral modification, pharmacotherapy, and surgical procedures have been employed in obesity treatment.[6-11]

In obesity, the most important source of pro-inflammatory cytokines is macrophages that infiltrate adipose tissue in response to fat cell growth, reduced blood flow, hypoxia, and tissue necrosis. These events collectively create a predisposition to systemic inflammation, a potential triggering factor in the pathogenesis of obesity-related morbidities. Several adipokines including adiponectin, leptin, resistin, visfatin, chemokine, tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, IL-8, IL-10, plasminogen activator inhibitor 1, monocyte chemotactic protein-1, and retinol binding protein-4 are involved in insulin resistance (IR) regulation. In healthy obese adults, increased transforming growth factor beta 1 and IL-6 inhibit cell differentiation and the function of adiponectin and leptin. Increased IL-6, IL-1 and TNF-α in obese individuals was associated with progression of several disorders including cardiovascular disease, hypertension and IR. Mortality is associated with increased circulating IL-6, IL-1β, TNF-α and IL-8.[12]

The aim of those treatments is to preserve the body weight for a long time after the suitable body weight is reached, and to prevent weight gain. In this study, we used Acti-Heart® as a monitoring tool of daily calorie consumption in a group of obese adolescents.

MATERIALS AND METHODS

A total of 14 cases with the age range of 10.1-16.6 years and puberty stage of III-IV, who were followed up at the Department of Pediatric Endocrinology and Metabolic Diseases in the Medical School of Çukurova University with the diagnosis of exogenous obesity were included in this study. These cases were recently diagnosed and had no known systemic, endocrine or neurological diseases. There were 13 children in the control group. Anthropometric measurements and detailed physical examinations were performed in all subjects.

Venous blood samples from participating cases were collected after a 12-hour overnight fast, before, in the middle of, and after the exercise and diet treatments. Fasting blood glucose, fasting insulin, low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, lipoprotein a, serum aspartate and alanin aminotransferase (AST and ALT), free-T4, thyroid stimulating hormone, insulin-like growth factor 1 (IGF-1), follicle-stimulating hormone, luteinizing hormone, estradiol (in females), testosterone (in males and females), C-reactive protein (CRP) (high sensitive), TNF-α, IL-6, IL-10, adiponectin, and visfatin levels were measured in the blood samples in the central laboratory at the Medical School of Çukurova University.

Serum transaminases were measured using the International Federation of Clinical Chemistry method, and the Roche Modular System/Integra 800 device and kit (Germany). Alanine aminotransferase and aspartate aminotransferase levels ≥40 IU/L were accepted as abnormal serum aminotransferase values. Serum lipid profile, HDL-C, LDL-C and VLDL-C measurements were performed using enzyme calorimetric methods and Roche modular system/integra 800 device and kit (Germany). Triglyceride levels were measured with GPO/PAP method and Roche modular system/integra 800 device and kit (Germany). Lipoprotein A, Apo A and Apo B were measured using immunoturbidimetric method and Roche modular system/integra 800 device and kit (Germany). Serum glucose was measured with hexokinase method and Roche modular system/integra 800 device and kit (Germany). Serum CRP was measured using nephelometric method and II Dade Behring device and kit. Cytokines, TNF-α, IL-6 and IL-10 were measured using micro-enzyme-linked immunosorbent assay (ELISA) automation system (Biosource kit, Belgium), and Triturus (Spain) micro-ELISA automation system. IGF-1 was measured with chemiluminescence method and immulate 2000 and the kit. Visfatin C- Terminal (Human) was measured in the serum using micro-ELISA method Triturus (France) automatic ELISA device (Human). EIA kit (Phoenix pharmaceuticals, USA) was used for the testing. Normal plasma range for visfatin is 0.1-1000 ng/mL. Adiponectin was studied in the serum by using micro-ELISA method, and Triturus (France) automated ELISA device. BioVendor Human Adiponectin ELISA kit was used for testing. IR and insulin sensitivity indices were calculated.

Electrocardiography (ECG), echocardiography, abdominal ultrasonography, were performed, and arterial intimal thicknesses were measured.

A skinfold caliper was used to determine body fat percentage, and measured values were put in the Yuhasz formula. Direct body fat measurement was performed using the bioelectrical impedance method. Resting metabolism rate was calculated using the calorimetric method.

The children we included in the study were given a motivational, dietary and exercise program for two months.

Regulation of the Diet Program

Patients and families were first informed about the forms to be filled out. Then, diet records were collected, in which the amounts of main and intermediate meals and beverages for one week were written with the criteria determined by the dietician, (such as tea glass, water glass, tablespoon). From these records, average calorie consumption was calculated by a pediatric dietician, taking into account weekdays and weekend days. Carbohydrate, protein, and fat ratios in the diet were also calculated. After this stage, the required daily energy amount was calculated for each patient according to age, gender, and ideal weight. The ideal weight, normal weight, height standard data, and puberty stages of school-age children were taken into consideration.

For each case, the diet was organized in accordance with the age, socioeconomic, and cultural conditions. Nutrients were selected, and the daily energy intake was organized as 50-55% carbohydrate, 15-20% protein, and 30% fat. In this way, the energy intake of the child was limited and food consumption was balanced. Dietary patterns, caloric intake, and energy distribution were obtained from the patients' seven-day nutritional records. Nutritional mistakes and deficiencies were discussed with the patients. The results of this dietary approach were explained in detail. In patients who were not morbidly obese, a balanced diet suitable for the required weight was given. In morbidly obese patients, short-term energy restriction was applied. The fact that the patients had not completed their growth was taken into consideration. Patient's daily energy intake was reduced by 200-500 calories. Patients were checked by a dietitian before, during, and at the end of the study. During the controls, it was detected that some subjects wanted to get faster results, and tried to consume fewer calories than the calories in the given diet. These patients were interviewed again, and their mistakes were corrected.

Daily Calorie Expenditure

Acti-Heart® is a light and portable device which records data about heart rate and physical activities at minute intervals via two ECG electrodes placed on the chest. The daily caloric expenditure of the patients was measured before and at the end of the study with the Acti-Heart® version 2,000.10 (Mini Mitter Company, Inc. USA) device (Figure 1) by entering the age, gender, weight and height data of the patients (covering two days of caloric expenditure on weekdays and weekends). The obtained data, including information about age, gender, weight, and height, were recorded on the computer, and then calculations were performed using a pre-existing program.

It was strongly emphasized to patients they should not perform any activity other than their normal activities during the time the device was worn. Daily calorie intake was calculated using a one-week diet recorded at home. Meal plans were prepared considering the age, socioeconomic conditions, and cultural characteristics of each patient.

A two-month home exercise program, which was based on basal heart rate values, was scheduled. A follow-up chart for exercise pulses, which was calculated for each age-group, was prepared. All measurements were performed at the beginning, the middle, and the end of the treatment.

Ethical Statements

The study was approved by Çukurova University Faculty of Medicine Ethics Committee (approval number: 2008-15, dated: 03.06.2008). The study was performed in accordance with the ethical rules based on the principles of the Helsinki Declaration. Written informed consent forms were obtained (when appropriate) from the parents and the children.

Statistical Analysis

Data obtained from this study were analyzed using Statistical Package for Social Sciences for Windows, version 10 (IBM Inc., Armonk, NY, USA). Data were expressed as the mean ± standard deviation (SD), median (min.-max.). While evaluating the study data, in addition to descriptive statistical methods (mean ± SD), analysis of variance table test was used to compare the obese patient group and the control group. The parameters of the

Figure 1. Acti-Heart®

obese patient group that changed with exercise were evaluated with the paired samples t-test. The results were evaluated within the 95% confidence interval and the significance level was $p<0.05$.

RESULTS

In this study, 27 children (14 were obese, and 13 were healthy children) with the mean age of 12.92±1.94 (range: 10-17) years were included. Of the children, 14 (51.9%) were girls and 13 (48.1%) were boys. Out of the cases, 14 were obese, and 13 were non-obese healthy (control) children. The mean weight of the patient group was 87.96±22.31 kg (min.: 55, max.: 133 kg), and of the control group was 47.08±11.54 kg (min.: 28, max.: 66 kg). There was a statistically significant difference in body weights between patients and controls ($p=0.001$). The mean BMI in obese children was 34.35±5.23 (ranging from 28 to 45) kg/m^2, while it was 20.02±2.95 (ranging from 16 to 27) kg/m^2 in the control group; there was a statistically significant difference between the groups ($p=0.001$). Body measurements in the patient group before, in the middle, and at the end of the exercise and diet treatment are displayed in Table 1.

There were statistically significant differences in BMI, skinfold thickness, waist and hip measurement, and waist/hip ratio between pre- and post-treatment measurements. There was a significant difference in the body fat percentage between pre- and post-treatment calculations. The BMI values of the patients before, in the middle, and at the end of exercise and diet are displayed in Figure 2.

There were statistically significant differences in AST, ALT, VLDL-C, triglyceride, and total cholesterol measurements between pre- and post-treatment measurements (in the same order $p=0.015$, $p=0.029$, $p=0.015$, $p=0.013$, $p=0.028$).

When the correlation between obesity and adipokines was investigated, mean TNF-α level was detected as 1.66±2.33 pg/mL in obese children; it was 3.62±2.35 pg/mL in the control group. The difference was statistically significant. The mean IL-10 levels were 0.28±0.64 pg/mL and 5.61±8.84 pg/mL in obese children and the control group, respectively. The difference was statistically significant. Differences in hs-CRP, IL-6, adiponectin and visfatin values between patient and control groups were not considered significant. The comparison of adipokines between patient and control groups is provided in Table 2.

There was a significant difference in homeostasis model assessment of IR (HOMA-IR) measurements between pre- and

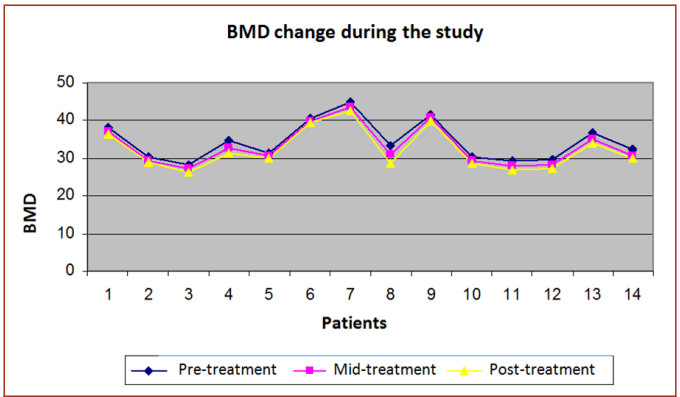

Figure 2. BMI values before, in the middle, and at the end of exercise and diet

BMI: Body mass index, BMD: Bone mineral density

Table 1. Body measurements in the patient group before, in the middle and at the end of exercise and diet treatment

Variables	Measurements	n	Mean	SD	p-value
BMI (kg/m^2)	Pre-treatment	14	34.35	5.23	0.001
	Mid-treatment	14	33.03	5.32	
	Post-treatment	14	32.10	5.35	
Waist (cm)	Pre-treatment	14	105.18	14.66	0.001
	Post-treatment	14	97.75	12.75	
Hip (cm)	Pre-treatment	14	109.61	10.83	0.003
	Post-treatment	14	106.79	10.80	
Waist/Hip ratio	Pre-treatment	14	0.97	0.09	0.029
	Post-treatment	14	0.91	0.08	
Skinfold thickness	Pre-treatment	14	25.43	2.43	0.003
	Post-treatment	14	23.83	2.06	
Body fat percentage (%)	Pre-treatment	14	33.76	11.77	0.007
	Post-treatment	14	31.98	11.49	

The parameters of the obese patient group that changed with treatment were evaluated by paired samples t-test. The significance level of the tests was set as $p<0.05$. SD: Standard deviation, BMI: Body mass index

post-treatment (p=0.001). Changes in IR with exercise and diet treatment in the patient group are shown in Table 3 and Figure 3.

When the calorie consumption of the patient group before and after the study, a statistically significant difference was detected between the two measurements (p=0.004). There was no statistically significant difference in the basal metabolism rates of the patient group before and after the study (p=0.194). Evaluation of energy consumption with exercise and diet in the patient group. It is shown in Table 4.

DISCUSSION

Obesity is a chronic energy metabolism disorder, which may ensue from excessive fat accumulation and cause severe problems physically, mentally. There is no obvious cause in the majority of obesity cases. These are defined as simple obesity or exogenous obesity. Obesity has become a public health problem

Table 2. Comparison of adipokines between patient and control groups

Variables	Measurements	n	Mean	SD	Median (min.-max.)	p-value
TNF-α (pg/mL)	Obese	14	1.66	2.33	0.50 (0-7)	0.029
	Control	13	3.62	2.03	0 (0-7)	
Hs-CRP (mg/dL)	Obese	14	6.29	3.28	5.82 (3-12)	0.059
	Control	13	9.77	12.75	3.30 (3-13)	
IL-6 (pg/mL)	Obese	14	1.70	1.79	1.25 (0-5)	0.161
	Control	13	1.06	1.08	2 (0-20)	
IL-10 (pg/mL)	Obese	14	0.28	0.64	0 (0-2)	**0.033**
	Control	13	5.61	8.84	1.80 (0-32)	
Adiponectin (µg/mL)	Obese	14	1.21	1.33	0.60 (0-4)	0.459
	Control	13	1.63	1.59	1.20 (0-7)	
Visfatin (ng/mL)	Obese	14	115.64	19.59	13.15 (3-638)	0.419
	Control	13	64.28	11.83	16.40 (0-403)	

Significance between control and obese group (One-Way ANOVA test). Significance level of the tests was accepted to be p<0.05. SD: Standard deviation, ANOVA: Analysis of variance, TNF-α: Tumor necrosis factor-alpha, Hs-CRP: High sensitivity-C-reactive protein, IL: Interleukin, min.-max.: Minimum-maximum

Table 3. Changes in IR in the patient group by exercise and diet treatment

Variables	Measurements	n	Mean	SD	p-value
Glucose (mg/dL)	Pre-treatment	14	84.08	6.66	0.109
	Post-treatment	14	79.38	6.59	
Insulin (mU/L)	Pre-treatment	14	23.25	7.46	0.358
	Post-treatment	14	22.24	7.84	
Glucose/Insulin	Pre-treatment	14	4.22	1.58	0.520
	Post-treatment	14	4.31	1.70	
HOMA-IR	Pre-treatment	14	4.80	1.43	**0.001**
	Post-treatment	14	2.38	1.33	

The parameters of the obese patient group that changed with treatment were evaluated by paired samples t-test. The significance level of the tests was accepted as p<0.05. SD: Standard deviation, HOMA-IR: Homeostasis model assessment of insulin resistance

Table 4. Evaluation of energy consumption in the patient group by exercise and diet

Variables	Measurements	n	Mean	SD	p-value
Basal metabolism rate	Pre-treatment	14	1675.69	438.21	0.194
	Post-treatment	14	1782.29	508.66	
Daily calorie consumption	Pre-treatment	14	1254.36	491.80	**0.004**
	Post-treatment	14	1524.71	546.93	

The parameters of the obese patient group that changed with treatment were evaluated by paired samples t-test. The significance level of the tests was accepted as p<0.05. SD: Standard deviation

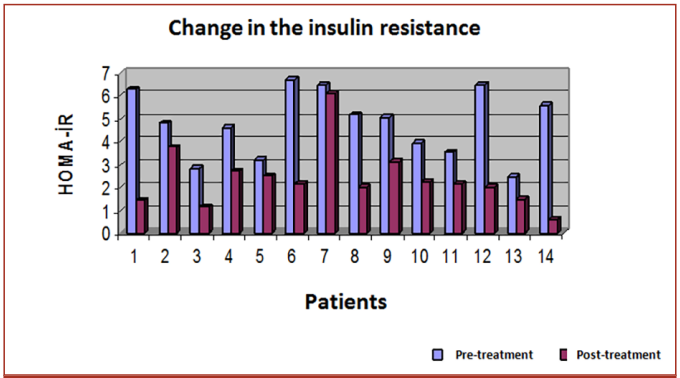

Figure 3. Changes in IR by exercise and diet
IR: Insulin resistance

all over the world with its increasing prevalence in the last two decades, especially in the Western populations.[13,14] The increase in obesity frequency in children is parallel with that in adults. This is caused by fats, carbohydrates, and fast-foods becoming more prominent among modern dietary habits, and children preferring to watch television and play computer games, rather than performing physical activities.[15,16] Obesity and the severe complications that this pathological condition may lead to have increased the interest in and need for effective, easily applicable, and simpler methods to prevent and treat obesity. Diet, exercise, and behavioral motivation are highly important and effective approaches.[17,18] If exercise treatment is accompanied by diet and behavioral modifications in obese patients, it causes more weight loss than diet alone. Hensrud et al.[19] conducted a two-year study by dividing people into diet only, exercise only, and diet plus exercise groups. In the diet plus exercise group, a mean, 13 kg weight loss was observed among 24 obese women after 1 year. While there was a 6 kg loss in the exercise only group, a 13 kg weight gain was observed in the diet only group.[19]

When the changes in lipid profile in the obese patient group before and after exercise were compared, significant decreases were found in total cholesterol, triglyceride, and and VLDL-C levels. There was no statistically significant difference between HDL-C, LDL-C, APO A, APO B, and lipoprotein measurements. In our study, as in the study of Kim et al.,[20] no significant difference was found between the values of HDL-C and LDL-C after diet and exercise treatment. We think that the small number of patients included in the study and the short duration of exercise may have caused this difference. Similar to the study of Kang et al.,[21] no significant changes were found in HDL-C, LDL-C, Apo A, Apo B and lipoprotein A levels with diet and exercise in our study.

When the relationship between obesity and liver function tests was investigated in our study, a statistically significant difference was found in ALT levels in obese children. Similar to the study of Li et al.,[22] no significant difference was found in AST measurements in our study. When AST and ALT values before and after exercise were compared in the obese patient group, a statistically significant decrease was found between the two measurements. This finding supports the view that exercise improves liver function by regulating energy and lipid metabolism. Jung et al.[23] found significant decreases in TNF-α and IL-6 levels and significant increases in IL-10 and adiponectin levels in obese individuals after a 12 week exercise program.

In the study by Kim et al.,[20] IL-6, TNF-α and hs-CRP levels were found to be significantly elevated in obese individuals, whereas adiponectin levels were found to be significantly lower. While adiponectin levels were found to be low in the same individuals after exercise, no significant difference was found in IL-6, TNF-α, and hs-CRP levels.[20] In our study, TNF-α and IL-6, which are inflammation markers, were found to increase after diet and exercise, contrary to expectations. However, the level of IL-10, an anti-inflammatory cytokine, was found to be lower in obese children compared to the control group, as expected. It increased with exercise. In our study, we attributed the increase in IL-6 and TNF-α to the effect of exercise on muscles, noting that IL-6 and TNF-α are myokines released from muscles during exercise, which demonstrates the effectiveness of exercise by an increase in their levels.[24,25]

In our study, when serum adiponectin levels were examined, no significant difference was found in obese children compared to the control group, nor was there a significant difference in obese children after exercise compared to before exercise. We think that the discordance in adiponectin levels in this study may be related to the insufficient number of patients included in the study, and the short duration of exercise. Furthermore, we suggest that longitudinal studies should be performed in large patient groups in the future to obtain clearer data.

In our study, we did not find a significant difference in serum visfatin levels in obese patients compared to the control group; however, we found a significant decrease in visfatin levels with exercise in obese children. This finding supports the view that obesity reduction may be due to the positive effect of exercise, which has been previously emphasized in the literature.

Crouter et al.[26] performed a study on energy consumption measurement and the reliability of Acti-Heart® in adults. The study was performed on 48 patients (24 males and 24 females; mean age: 35 years). Patients were divided into three groups according to their lifestyles and exercising habits (sedentary time, time at home, and exercising), and concomitant oxygen consumption of patients was measured. Six routine activity programs were scheduled for patients as 10 minutes of physical activity and 1-2 minutes of rest. Heart rate and energy consumption were

measured by Acti-Heart® by estimating heart activity, and the recorded data during all activities were transferred to the computer. In the meantime, energy consumption was measured during each routine activity by using the portable indirect calorimetric method (Cosmed K4b2, Italy). The study is valuable as it has indicated the reliability of measurement by Acti-Heart®.[26] In another study performed by Barreira et al.,[27] energy consumption during short-term physical activity was measured in 34 healthy subjects with the mean age of 21.8 months using Acti-Heart®, and it was reported that there was an increase in daily calorie consumption after the exercise program, which was measured by Acti-Heart®. Changes in daily calorie consumption were measured in obese adolescents before and after a triple treatment program of behavioral motivation, diet, and exercise for one day per week and two days on the weekend. A significant difference was determined in daily calorie consumption of obese patients, before and after treatment ($p=0.004$). Thus, we believe that by using Acti-Heart® we have objectively assessed energy expenditure in the diagnosis, treatment and follow-up of pediatric obesity. Moreover, we think that since the study results showed significant correlations between energy consumption measured before and after treatment by Acti-Heart® and BMI, skin fold thickness, body fat percentage, waist/hip ratio, hepatosteatosis, HOMA-IR, plasma lipid, IL-6, IL-10, TNF-α, hs-CRP, and visfatin levels, further research should explore these correlations in greater detail.

CONCLUSION

In our study, we showed that energy consumption increases during obesity treatment in adolescence by changing the lifestyle through behavior, diet, and exercise approaches. We used Acti-Heart® to assess calorie consumption in the diagnosis, treatment and follow-up of adolescent obesity. We also showed that Acti-Heart® was an easily applicable, non-invasive, cost-effective (no additional cost other than electrodes) device, and it could gather information about the energy consumption in every part of daily life, including sleeping and sports. Moreover, it was well-correlated with other parameters in obesity treatment follow-up; therefore, it is also an important and practical evaluation method. However, we believe that larger studies should be performed to support our conclusions.

Ethics

Ethics Committee Approval: The study was approved by Çukurova University Faculty of Medicine Ethics Committee (approval number: 2008-15, dated: 03.06.2008).

Informed Consent: Written informed consent forms were obtained (when appropriate) from the parents and the children.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.Ö., S.E., A.K.T., B.Y., N.Ö.M., Concept: İ.Ö., E.M., S.E., G.D., A.K.T., B.Y., N.Ö.M., Design: İ.Ö., E.M., S.K., G.K., G.D., N.Ö.M., Data Collection or Processing: İ.Ö., S.K., G.K., K.A., G.D., A.K.T., B.Y., N.Ö.M., Analysis or Interpretation: İ.Ö., E.M., S.K., G.K., S.E., K.A., F.T., F.G., G.D., A.K.T., B.Y., N.Ö.M., Literature Search: İ.Ö., E.M., F.T., F.G., G.D., A.K.T., B.Y., N.Ö.M., Writing: İ.Ö., E.M., N.Ö.M.

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ORIGINAL ARTICLE

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Analysis of Laboratory and Demographic Data of Late Diagnosed Phenylketonuria Cases

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Abstract

Objectives: In this study, it was aimed to evaluate the clinical, demographic, and laboratory data of the patients we followed up with late diagnosed phenylketonuria (PKU). In addition, the relationship between the age of onset of treatment and neuromotor development will be evaluated.

Materials and Methods: In this study, patients diagnosed with PKU and followed in the Pediatric Metabolism Outpatient Clinic were retrospectively examined. Cases diagnosed late were evaluated.

Results: We determined that 25 of our patients with PKU received a late diagnosis. Of these patients, 19 had classical PKU, and 6 had a mild PKU phenotype. Eight of our cases were female and 17 were male. The mean age at diagnosis of patients was 26.3±38.1 (range, 2-192) months. The mean age of the patients at the last evaluation was calculated to be 13.1±5.3 (range, 3.8-21.3) years. At the last evaluation, the phenylalanine level of the patients was 465.3±275.7 µmol/L in mild PKU and 779.1±449.4 µmol/L in classical PKU. Fifteen of our cases had global developmental delay, six had moderate developmental delay, and four had mild developmental delay. Twenty-one of our cases received diet therapy, and four of our cases received large neutral amino acid therapy.

Conclusion: It causes severe neurological problems in patients who are diagnosed late or undiagnosed. Therefore, close follow-up is important in the diagnosis and treatment phase of the disease. Close follow-up is essential to ensure that patients diagnosed with PKU can receive their treatment in the early period.

Keywords: Phenylketonurias, Therapeutics, Nervous System Diseases

INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive metabolic disease caused by the deficiency of phenylalanine hydroxylase, an enzyme that converts phenylalanine, an essential amino acid, to tyrosine in the liver.[1] The phenylalanine hydroxylase enzyme is encoded by the phenylalanine hydroxylase *(PAH)* gene, and its cofactor is tetrahydrobiopterin. The gene encoding the PAH enzyme is localized in the q22-q24.[1] band region on the long arm of chromosome 12.

The frequency of PAH deficiency varies according to ethnicity and geographical region. Due to the high rate of consanguineous marriages in Türkiye, PKU occurs at a frequency of 1/4370. Neonatal PKU screening in our country was first conducted as a pilot study in 1983. It was included in the screening scope nationwide after 1994.[2] In our country, blood samples are taken from babies twice within the scope of neonatal screening. The first blood sample is taken before hospital discharge, and the second is taken one week later. Today, PKU is one of the diseases that is recommended for screening because it is highly prevalent and treatable. Early diagnosis and treatment can prevent irreversible damage in this disease.

In PKU, phenylalanine and its metabolites cause structural brain damage, severe intellectual disability, and psychiatric disorders

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as a result of neurotoxic effects.[3] Early diagnosis and treatment are necessary to prevent or reduce the symptoms of the disease. With the emergence of newborn screening programs, the most serious neuropsychiatric findings of the disease can be prevented. The clinical picture resulting from the *PAH* gene defect varies from mild hyperphenylalaninemia to classical PKU. A phenylalanine-restricted diet is the main treatment method. However, research on the treatment of PKU is continuing, and new treatment options are emerging that can reduce the burden of the difficult and restrictive diet on patients.

Patients with PAH deficiency do not have any clinical findings at birth. They usually apply to the hospital when they are 3-4 months old, suggesting these delays prompt the hospital visit. Late-diagnosed patients with classical PKU experience severe intellectual disability, microcephaly, ataxia, autism, convulsions, aggression, eczema-like skin lesions, and behavioural disorders.[4]

In this study, we aimed to evaluate the clinical, demographic, and laboratory data of patients we follow with late-diagnosed PKU. In addition, the relationship between the age of initiation of treatment and neuromotor development will be evaluated.

MATERIALS AND METHODS

In this study, patients who were followed up in the Pediatric Metabolism Outpatient Clinic between January 2021 and July 2023 and diagnosed with PKU were retrospectively examined. Late-diagnosed cases were evaluated. The patients included in the study were evaluated for age at diagnosis, follow-up period, height, weight, head circumference, gender, history of consanguinity between parents, clinical phenotype, plasma phenylalanine levels at admission, and metabolic control status during treatment and follow-up. These data were obtained from the patients' electronic files in the hospital information management system. Clinical, demographic, and laboratory data of all patients were analysed. *PAH* gene analysis was performed on all our patients, and biallelic variants were detected.

The blood phenylalanine levels of the patients were determined by taking 2 mL of blood in tubes containing ethylenediaminetetraacetic acid and using high-performance liquid chromatography in the Metabolism Laboratory. For mutation screening and genotyping of the patients, exons 1-13 of the *PAH* gene were examined by polymerase chain reaction) amplification, followed by DNA sequence analysis. Mutations caused by nucleotide changes, detected by DNA sequence analysis, were identified.

Blood dihydropteridine reductase activity and neopterin, and biopterin analyses were performed to evaluate BH4 metabolism disorders. The normal range for plasma phenylalanine is 60-120 µmol/L. If phenylalanine levels were >1200 µmol/L before treatment at the time of diagnosis, it was classified as classical PKU; if phenylalanine levels were between 600-1200 µmol/L, it was classified as mild PKU; and if phenylalanine levels were <600 µmol/L, it was classified as mild hyperphenylalaninemia. Speech, fine motor, gross motor, personal, and social skills of the patients were evaluated with developmental tests. According to the developmental tests, the patients were defined as having global, moderate, and mild developmental delay.

Each procedure was carried out in accordance with the ethical principles determined by the committee responsible for human experiments and the Declaration of Helsinki. Informed consent was obtained from each patient before participating in the study. Approval for the study was obtained from the University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (approval number: 162, dated: 09.09.2022).

Statistical Analysis

Descriptive statistics were presented including minimum, maximum, mean ± standart deviation, percentage, and frequency values. Categorical data were analyzed with the chi-square test. All data were transferred to the computer, and statistical analysis was performed using Statistical Package for the Social Sciences version 22.0 . A p-value of <0.05 was considered significant.

RESULTS

The highest plasma phenylalanine levels measured at the time of diagnosis were taken as the criterion in determining the phenotypes of the patients. It was determined that 25 of our patients with PKU were diagnosed late. Nineteen of these patients had classical PKU, and 6 had mild PKU. It was determined that 11 (44%) of our cases were excluded from the newborn screening program and applied to our pediatric metabolism clinic due to neuropsychiatric symptoms, and they were diagnosed with PKU. Two of the cases excluded from the newborn screening program were diagnosed due to a history of a sibling with PKU. It was observed that 14 (56%) of our cases were diagnosed through the newborn screening program, but their hospital admission was late.

Eight of our cases were female and 17 were male. The mean age at diagnosis of all patients was 26.3±38.1 months (range, 2-192) months. The mean age at the last evaluation of the patients was calculated as 13.1±5.3 (range, 3.8-21.3) years (Table 1). Thirteen (52%) of the patients were diagnosed and started on treatment before the age of one. There was consanguinity between the parents of 18 of our patients.

Table 1. Clinical and laboratory data of our late diagnosed PKU cases

Patient/ gender	Age at diagnosis (month)	Current age (years)	Presentation complaint	Phenylalanine levels at diagnosis (µmol/L)	Phenylalanine levels at last evaluation (µmol/L)	Diagnosis	Neurological status	Treatment	Genotype
1/M	12	11.2	Neonatal screening	1364	320	Classical PKU	Global developmental delay	Diet	IVS10-11G>A/ IVS10-11G>A
2/F	60	15.2	Sibling with PKU	1675	1400	Classical PKU	Global developmental delay	Diet	c.1222C>T/ c.1222C>T
3/M	48	12.7	Sibling with PKU	1563	1300	Classical PKU	Global developmental delay	Diet	c.143T>C/ c.143T>C
4/F	42	18.8	Developmental delay, tremor, microcephaly	1680	290	Classical PKU	Global developmental delay	Diet	c.1039C>T/ c.1039C>T
5/M	30	17.7	Developmental delay, autism	820	410	Mild PKU	Global developmental delay	Diet	c.781C>T/ c.781C>T
6/M	7	14.1	Neonatal screening	1828	210	Classical PKU	Mild developmental delay	Diet	c.194T>C/ c.194T>C
7/F	6	11.2	Neonatal screening	1223	620	Classical PKU	Moderate developmental delay	Diet	c.728G>A/ c.728G>A
8/M	6	8.4	Neonatal screening	1320	330	Classical PKU	Global developmental delay	Diet	c.838G>A/ c.838G>A
9/F	13	5.2	Neonatal screening	1625	215	Classical PKU	Moderate developmental delay	Diet	c.168G>T/ c.168G>T
10/M	8	21.1	Neonatal screening	1466	540	Classical PKU	Global developmental delay	LNAA	IVS10-11G>A/ IVS10-11G>A
11/M	10	11.7	Neonatal screening	917	580	Mild PKU	Moderate developmental delay	Diet	c.143T>C /c.143T>C
12/M	12	10.2	Neonatal screening	650	310	Mild PKU	Global developmental delay	Diet	c.1222C>T/ c.1222C>T
13/M	11	14.9	Neonatal screening	670	335	Mild PKU	Global developmental delay	Diet	c.781C>T/ c.781C>T
14/M	9	13.1	Neonatal screening	1380	943	Classical PKU	Mild developmental delay	Diet	IVS10-11G>A/ IVS10-11G>A
15/M	30	21.3	Epilepsy	743	964	Mild PKU	Mild developmental delay	LNAA	c.782G>A/ c.782G>A
16/F	7	6.1	Neonatal screening	2280	520	Classical PKU	Mild developmental delay	Diet	c.1222C>T/ c.1222C>T
17/F	24	20.1	Epilepsy	1420	850	Classical PKU	Global developmental delay	LNAA	c.143T>C/ c.143T>C
18/M	14	8.3	Developmental delay	866	193	Mild PKU	Global developmental delay	Diet	IVS10-11G>A/ c.782G>A
19/M	24	18.2	Epilepsy	1716	1250	Classical PKU	Global developmental delay	Diet	IVS10-11G>A/ c.1222C>T

Table 1. Continued

Patient/ gender	Age at diagnosis (month)	Current age (years)	Presentation complaint	Phenylalanine levels at diagnosis (µmol/L)	Phenylalanine levels at last evaluation (µmol/L)	Diagnosis	Neurological status	Treatment	Genotype
20/M	24	11.9	Epilepsy	1601	1391	Classical PKU	Global developmental delay	Diet	IVS10-11G>A/ c.1222C>T
21/F	4	3.8	Neonatal screening	1341	261	Classical PKU	Moderate developmental delay	Diet	c.1039C>T/ c.1039C>T
22/M	3	5.9	Neonatal screening	1292	719	Classical PKU	Moderate developmental delay	Diet	c.168G>T/ c.168G>T
23/M	2	7.3	Neonatal screening	1334	1081	Classical PKU	Moderate developmental delay	Diet	c.168G>T/ c.1039C>T/
24/F	192	18.6	Epilepsy, microcephaly, autism, tremor	1409	1420	Classical PKU	Global developmental delay	Diet	c.838G>A/ c.728G>A
25/M	60	20.2	Epilepsy, autism	1480	1144	Classical PKU	Global developmental delay	LNAA	IVS10-11G>A /c.838G>A

The phenylalanine level of the patients at the time of diagnosis was 777.6±107.7 µmol/L in mild PKU and 1526.1±246.8 µmol/L in classical PKU (Table 1). The phenylalanine level of the patients at the final evaluation was 465.3±275.7 µmol/L in mild PKU and 779.1±449.4 µmol/L in classical PKU (Table 1). The most common IVS10-11G>A mutation was found in patients. This allele was followed by the c.1222C>T (p.Arg408Trp) and c.143T>C (p.Leu48Ser) variants, respectively. Fifteen of our cases had global developmental delays, 6 had moderate developmental delays, and 4 had mild developmental delays. When we grouped the patients according to the severity of neurological findings, no statistically significant difference was found between the groups in terms of phenylalanine levels at the time of diagnosis.

In the diet treatment, our patients were given total protein intake 2-2.5 g/kg/day for the first year, 1.1-1.7 g/kg/day for ages 1-11, 1 g/kg/day for ages 12-15, and 0.9 g/kg/day for adults. The phenylalanine content of the diet was set at 130-400 mg/day for the first year, 200-400 mg/day for ages 1-11, 350-800 mg/day for ages 12-15, and 450-1000 mg/day for adults. Diet treatments were organized with natural foods and special formula foods that do not contain phenylalanine. Twenty-one of our cases received diet treatment; and 4 of our cases received large neutral amino acid (LNAA) treatment (Table 1). LNAA supplements were administered to adult patients who did not adhere to dietary treatment.

DISCUSSION

In our country and the countries in this region (Middle East, West Asia, South Asia, North Africa), the frequency of consanguineous marriages is high. PKU and other autosomal recessive metabolic disorders are more frequently observed in societies where consanguineous marriages are high. In a study conducted in our country in 1993, the frequency of PKU was determined to be 1/4370, and the rate of consanguineous marriage was 21.5%.[5] The frequency of the disease varies considerably worldwide. In Europe, the frequency of PKU is 1/3000-1/30000, with an average of 1/10000 reported.[3,6] In our country, newborn screening for PKU is performed during the neonatal period. The diagnosis is confirmed by the determination of plasma phenylalanine level and *PAH* gene analysis. PKU screening has been performed in our country since 1993. However, in the study conducted by Tezel et al.,[2] the newborn screening rate was 4.7% in 1987, and this rate increased to 95% in 2008. In patients detected through newborn screening, treatment can be started in the second/third week of life.

The cases we present in this study were diagnosed late, and treatment was started after the second month of life. It was determined that 25 of our patients who have PKU and whom we followed up were diagnosed late. Nineteen of these patients

had classical PKU, and six had mild PKU phenotypes. All of our patients were born after the newborn screening program started, but only 56% were screened. 44% of our cases were not screened. In cases where screening could not be done, the diagnosis was made after the onset of neurological and psychiatric symptoms, during the examination. It was determined that our cases included in the screening program were reported late or applied late to the metabolism centre late despite being reported. It was determined that the instances of incomplete screening were generally families who gave birth at home and lived in rural areas.

Neuromotor retardation, microcephaly, and epilepsy can be seen in cases in which the treatment started late. High levels of phenylalanine and its metabolites can cause musty body odour and eczema. Tyrosinase inhibition and low tyrosine levels also cause loss of pigmentation in the skin and hair. In addition, behavioural disorders, aggressive behaviour, depression, and anxiety can be seen.[7-9] Our cases have epilepsy, behavioural disorders, and neuromotor delay. It is thought that cognitive problems seen in PKU are related to prefrontal dopamine depletion.[10] Phenylalanine competes with tyrosine at the blood-brain barrier, but phenylalanine passes through at high phenylalanine levels. CSF tyrosine levels decrease, and adequate dopamine synthesis cannot be achieved.[10] In addition, the negative effect of high phenylalanine levels on glutamate receptor function leads to brain dysfunction in patients with PKU.[11,12] Glushakow et al.[12] have shown that high phenylalanine levels significantly suppress the function of glutamate receptors in excitatory synapses.

The aim of treating PKU is to reduce plasma phenylalanine levels. A multidisciplinary approach is important in the treatment of patients with PKU. Treatment should be started as soon as possible in infants with plasma phenylalanine concentrations above 360 µmol/L. In the treatment of the disease, a protein-restricted diet containing low phenylalanine, sapropterin dihydrochloride, LNAAs to a protein-restricted diet, and phenylalanine ammonium lyase enzyme therapy are used.[4,13,14] However, attention should be paid to the protein intake required for optimal growth and development. It is recommended that treatment be continued throughout life. The aim of treatment is to reduce plasma phenylalanine levels, increase natural protein tolerance, maintain normal neuropsychological development, and provide a good quality of life. Twenty-one of our patients receive diet therapy. The other cases receive LNAA therapy. Patients received tyrosine supplements as needed according to their plasma tyrosine levels.

LNAA treatment is not recommended for young children or during pregnancy but is an option for adults who are not in good metabolic control and are not compliant with dietary therapy.[15] LNAAs (arginine, histidine, isoleucine, leucine, lysine, methionine, threonine, tryptophan, tyrosine, and valine) compete with phenylalanine at the blood-brain barrier. Therefore, LNAA supplementation can significantly reduce phenylalanine uptake in the brain, in patients.[16] In this study, every patient who received LNAA supplementation was an adult who did not comply with dietary therapy.

Study Limitations

Our study has some limitations. First, neuroimaging could not be performed in most of our patients. Cooperation with the patients for MRI was not possible due to their neurological impairment. In addition, neuroimaging could not be performed due to the socioeconomic status of some families. Secondly, since our study is retrospective, the patients' treatment interruption status could not be fully evaluated.

In our country, PKU is a treatable metabolic disease that is included in the newborn screening program. It causes severe neurological problems in patients who are diagnosed late, or cannot be diagnosed. Therefore, close monitoring is important during the diagnosis and treatment phase of the disease. Close monitoring is essential to ensure that patients diagnosed with PKU receive their treatment at an early stage.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (approval number: 162, dated: 09.09.2022).

Informed Consent: Informed consent was obtained from each patient before participating in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.B., A.E.B., Concept: H.B., A.E.B., Data Collection or Processing: H.B., Analysis or Interpretation: H.B., A.E.B., Literature Search: H.B., A.E.B., Writing: H.B.

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CASE REPORT

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A Methylmalonic Acidemia Patient Mimicking Diabetic Ketoacidosis and Long-Term Follow-Up

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Abstract

Methylmalonic acidemia (MMA) is the most common inherited type of organic acidemia. It has a diverse presentation in older infants without any initial apparent symptoms. MMA sometimes presents with sudden metabolic decompensation, which may mimic common emergencies like diabetic ketoacidosis (DKA); without early recognition, it can be fatal. In this case, we aimed to emphasize that less common diagnoses such as organic acidemia should be kept in mind in infants with severe acidosis and metabolic decompensation, or in patients with an atypical clinical course to prevent serious morbidities and even death. We report a case of MMA in an infant who presented acutely mimicking DKA and underwent long-term surveillance. An 8.5-month-old girl, the first child of an unrelated family, was admitted with complaints of vomiting and hyperglycemia and metabolic acidosis were detected. In her history, complementary feeding started at 7 months, and she had one hospital admission at 7 months due to vomiting, which improved with intravenous fluid therapy. A diagnosis of DKA was made, and appropriate fluid therapy and insulin infusion were started. However, despite achieving normoglycemia, the anion gap (AG) remained high, and metabolic acidosis persisted. Due to ongoing drowsiness and high serum ammonia levels (215 µg/dL), a metabolic disorder was suspected, and peritoneal dialysis was initiated. Tandem mass spectrometry analysis showed markedly elevated C3 propionylcarnitine levels and increased C3/C2 and C3/free carnitine ratios, while urinary organic acid analysis revealed a significant increase in methylmalonic acid excretion, along with a marked rise in 3-hydroxypropionate and methylcitrate. *MUT* gene analysis revealed a homozygous mutation c.360_361insT (p.K121*), confirming the diagnosis of MMA. Long-term follow-up has shown a progressive decline in her estimated glomerular filtration rate (eGFR), with even lower levels observed during acidosis attacks. Inborn errors of metabolism, especially organic acidemia, should be suspected in any infant presenting with severe high AG metabolic acidosis. MMA is also associated with chronic tubulointerstitial nephritis and a progressive decline in GFR.

Keywords: Methylmalonic Acidemia, Hyperglycemia, Diabetic Ketoacidosis, Glomerular Filtration Rate

INTRODUCTION

Methylmalonic acidemia (MMA), a form of organic acidemia, occurs due to a defect in the methylmalonyl-CoA mutase (MCM) enzyme, which is responsible for converting methylmalonyl-CoA to succinyl-CoA.[1] A partial or complete deficiency of the cobalamin-dependent MCM enzyme leads to the accumulation of methylmalonyl-CoA, resulting in a significant increase in the excretion of methylmalonic acid (MMA) in both blood and urine.[2] MMA affects around 1 in every 50,000 to 80,000 babies. It is more prevalent in nations with high levels of consanguinity and lack of newborn screening, such as economically disadvantaged countries.[1] Patients often present between 1 month and 1 year old with symptoms such as poor feeding, vomiting, dehydration, shock, hypoglycemia, hyperammonemia, and high anion gap (AG) metabolic acidosis, which can progress to coma or death if not treated. The mild form of the disease may occur in infancy and childhood.[3] MMA can occur unexpectedly in older infants, mimicking septic shock or diabetic ketoacidosis (DKA) and be potentially lethal if not detected early.[4] We reported a case of MMA in a newborn with severe high AG metabolic acidosis that mimicked DKA, despite no early symptoms.

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CASE REPORT

An 8.5-month-old female patient, with no prior medical history, presented with a complaint of projectile vomiting including the contents of her meals, for the past four days. There was no associated fever, diarrhea, or abdominal pain. About two days later, respiratory distress developed, her feeding gradually worsened, and she had frequent urination, without a foul odor. There was no history of drug or substance intake. The patient's family history revealed that the parents, who are not related but are from the same village, had their first child with a term birth. She had a history of meconium aspiration and was followed in the neonatal intensive care unit for one week. Complementary feeding started at 7 months, and she had one hospital admission at 7 months due to vomiting, which improved with intravenous fluid therapy. Upon examination, she was found to be dehydrated.

Laboratory tests showed a blood glucose level of 234 mg/dL, and +2 ketones in the urinalysis, and metabolic acidosis (pH: 7.01, HCO_3: 6.4 mmol/L). A diagnosis of DKA was made, and appropriate fluid therapy and insulin infusion were started. However, despite achieving normoglycemia, the AG remained high (28), and metabolic acidosis (pH: 7.18, pCO2: 20 mmHg, HCO_3: 10.4 mmol/L) persisted. In addition, insulin, and C-peptide values were also normal. Due to ongoing drowsiness and high serum ammonia levels (215 µg/dL), a metabolic disorder was suspected, and peritoneal dialysis was initiated, which led to the correction of both the acidosis and hyperammonemia. To clarify the etiology before starting peritoneal dialysis, blood and urine samples were taken for Tandem mass spectrometry (MS), and urinary organic acid analysis, and the patient was referred to our Pediatric Metabolism and Nutrition Department for further investigation and management. On physical examination at the time of admission, body temperature was 36.7 °C; pulse was 118 beats per minute; respiratory rate was 40/min; blood pressure was 95/55 mmHg; body weight was 7400 grams [<3 p, -1.12 standard deviation (SD)]; height was 64 cm (<3 p, -1,96 SD); oxygen saturation was 97%, with no significant findings on systemic examination and no specific odor. Initial laboratory results included hemoglobin: 9.2 g/dL, total leukocyte count: 8240/mm^3 with 68% neutrophils, platelet count: 251,000/mm^3, C-reactive protein: 8 mg/dL, venous blood gas: pH 7.35, HCO_3: 20.3 mmol/L, AG: 24.5 mmol/L, lactate: 1.2 mmol/L, blood glucose: 75 mg/dL, serum electrolytes: normal, blood urea nitrogen: 7.93 mg/dL, creatinine: 0.4 mg/dL, serum calcium: 7.6 mg/dL, and glomerular filtration rate: 72. Urine analysis showed pH: 5.5; density: 1022; glucose 2+; protein 1+; and ketones 2+. Serum ammonia was 68 µg/dL, lactate was 13 mg/dL, and pyruvate was 0.7 mg/dL; all were normal. Amino acid levels in both urine and blood were normal. In pre-dialysis tests at the external facility, Tandem MS analysis showed markedly elevated C3 propionylcarnitine levels and increased C3/C2 and C3/free carnitine ratios. Urinary organic acid analysis revealed a significant increase in MMA excretion, along with a marked rise in 3-hydroxypropionate and methylcitrate. Based on these findings, the patient was diagnosed with MMA, and treatment with 100 mg/kg levocarnitine and 1 mg hydroxocobalamin was initiated.

Her feeding was adjusted to a branched-chain amino acid-deficient special formula, and isoleucine powder supplementation was provided upon identifying a low isoleucine level in her blood amino acids. *MUT* gene analysis revealed a homozygous mutation c.360_361insT (p.K121*), confirming the diagnosis of MMA. Genetic testing showed that both parents were heterozygous for the same mutation.

After diagnosis, the patient had four episodes of metabolic acidosis, two of which were resistant. At the age of 3, she developed metabolic acidosis, hyperuricemia, and hyperkalemia. In addition to her existing treatment, Shohl's solution, anti-potassium therapy, and allopurinol were started. At the age of 5, the patient experienced a refractory metabolic acidosis and hyperammonemia attack accompanied by delirium, during which antihypertensive medications were added to her treatment. Long-term follow-up has shown a progressive decline in her estimated glomerular filtration rate (eGFR), with even lower levels observed during acidosis attacks. The informed consent of the patient was obtained from her family.

DISCUSSION

We present a case of an infant with MMA who experienced unexpected decompensation associated with high AG and severe metabolic acidosis without any preceding signs or symptoms. In this report, the infant presented with hyperglycemic DKA with a weak insulin response. Due to the persistence of DKA, an underlying metabolic issue was investigated. Hyperglycemia is a rare but fatal MMA symptom that resembles DKA.[5,6] Although hyperglycemia is an infrequent MMA manifestation,[7] there have been described cases of severe and prolonged metabolic acidosis and hyperglycemia despite substantial insulin doses. Diabetes is the most prevalent cause of DKA, but it responds well to standard treatment; thus, additional causes of acidosis/hyperglycemia should be examined in poor responders.[8]

Organic acidurias (OAs) should be included in the differential diagnosis, especially in countries where national newborn screening is not implemented. Determining the etiology of hyperglycemic DKA is important and can lead to a good outcome.[9] The unusual presentation of our patient, mimicking DKA, reminds us of the wide spectrum of clinical signs of organic acidemia. In infants with severe acidosis and metabolic decompensation, or with atypical clinical course, there should

be a suspicion of a less common diagnosis, such as organic acidemia, to prevent severe morbidities and even death.[10]

Despite significant advancements in treatment, long-term complications such as developmental delay, neurological disorders due to degeneration of the basal ganglia, interstitial nephritis, progressive renal failure, pancreatitis attacks, and cardiomyopathy are commonly observed.[11-13] Impaired kidney function is a well-documented long-term complication of MMA and occurs more frequently than in other organic acidemias. The onset of kidney dysfunction in MMA is related to the molecular subtype. Mut^0 patients are typically affected at an earlier age compared to CblB patients, while CblA and mut- patients may experience kidney issues in later stages of life.[2,14,15] The pathogenesis of kidney damage associated with MMA is not well understood.

Kidney involvement in MMA patients can be both tubular; [proximal renal tubular acidosis (RTAs), impaired urine acidification and concentration ability, and hyporeninemic hypoaldosteronism] and glomerular (chronic interstitial nephritis).[16] Mitochondrial dysfunction appears to play a key role in the pathomechanisms of kidney damage in MMA. In a metabolic acidosis environment, increased ammonia production in the proximal tubule has been suggested as a potential mechanism contributing to the worsening of kidney function.[17] In a rat model, it has been observed that nitrogen nucleophiles, such as ammonia, cause kidney damage and induce chronic tubulointerstitial inflammation through the activation of an alternative complement pathway. Additionally, the activation of the renin-angiotensin system (RAS) plays a role in the pathogenesis of kidney dysfunction associated with metabolic acidosis. This suggests that both toxic metabolites like ammonia, and systemic pathways like RAS, contribute to the kidney damage seen in conditions such as MMA, where metabolic derangements lead to renal complications.[18]

In a study conducted by Şeker Yılmaz et al.[19] from our country, 12 out of 37 isolated MMA patients (32%), were found to have kidney involvement. One patient, despite good metabolic control, exhibited early-onset and rapidly progressing kidney complications, particularly RTA type 4 and stage 3 chronic kidney disease.

In MMA patients, monitoring kidney functions is strongly recommended. Serum creatinine, as a surrogate marker of kidney function, may be misleading, because in MMA patients with protein deficiency, a reduction in muscle mass likely results in an overestimation of GFR. Other kidney function markers, such as serum cystatin C, may better reflect the true eGFR and provide a more accurate assessment of renal function in these patients.[20]

During the follow-up of our patient, we observed that the serum creatinine levels began to rise around the age of one, peaked at the age of five, and then stabilized. During the long-term follow-up, the eGFR, calculated using the Schwartz formula, progressively decreased to a value of 65.66 mL/min/1.73 m² at the age of eight. Additionally, during episodes of acidosis, the eGFR was found to be even lower (Table 1).

Blood pressure monitoring should be an integral part of kidney function assessments in patients with conditions like MMA. Hypertension can be a significant complication in these patients and may contribute to the progression of kidney dysfunction, making its early detection and management crucial for preserving renal health.[2] In the case of our patient, during a resistant metabolic acidosis and hyperammonemia episode at the age of five accompanied by a delirium episode, antihypertensive medication was added to the existing treatment.

Combined liver and kidney transplantation appears to be an effective treatment for renal failure in MMA, and it can result in normal kidney function even 10 years after transplantation.[21,22] Kidney transplantation improves kidney function shortly after

Table 1. Summary of the patient's laboratory values in follow-up

Age (Year)	BUN (5-18 mg/dL)	Creatinin (0.4-0.6 mg/dL)	eGFR* (mL/min/1.73 m²)	Cloride (98-107 mEq/L)	Uric acid (3.4-7 mg/dL)	Urine keton	Urine MMA
1	**34**	0.25	143	**111**	3.09	+	-
2	**26.85**	**0.61**	**76.63**	**106**	**9.39**	-	
3	13	0.51	91.66	98	5.3	-	-
4	14	0.53	88.20	104	3.7	-	-
5	**45**	**0.97**	**54.43**	**107**	**8.1**	++	
6	17	**0.77**	**76.071**	96	5	-	-
7	19	**0.89**	**72.30**	92	4	-	-
8	9.2	**0.98**	**65.66**	105	3.4	-	-

BUN: Blood urea nitroge, eGFR: Estimated glomerular filtration rate, MMA: Methylmalonic acid

the transplant, and, in some cases, even years after the procedure (ranging from 1.5 to 14 years). However, it has also been reported that nephropathy and renal failure can recur after kidney transplantation.[23,24] While a few patients show normal kidney function even 15 years after transplantation, some patients develop progressive kidney failure after transplantation. Liver transplantation does not appear to correct a non-functional kidney.[22,25,26]

In countries like Türkiye, where national newborn screening is not implemented, OAs should be included in the differential diagnosis when high AG metabolic acidosis is accompanied by hypo/hyperglycemia,. It is especially important to remember that all patients with MMA are at risk of developing kidney failure during the long-term course of the disease.

Ethics

Informed Consent: The informed consent of the patient was obtained from her family.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.K.Y., Concept: G.K.Y., Design: M.A.K., G.K.Y., Data Collection or Processing: M.A.K., Analysis or Interpretation: M.A.K., G.K.Y., Literature Search: M.A.K., Writing: G.K.Y.

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TECHNICAL NOTE

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An Overview on Selenoproteins and Their Functions

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Abstract

Selenium, is a vital trace element required by many living organisms. It is mainly incorporated in selenoproteins functioning in boosting immune system, reducing inflammation, decreasing cardiovascular disease and inhibiting cancer progression. Fifty different selenoprotein families have been identified. They fulfill a broad range of physiological roles, notably functioning as antioxidants and participating in thyroid hormone metabolism. They are key regulators of stress responses, metabolism, and immunity. Selenoproteins will may be utilized in the treatment of various pathologies, including cancer, diabetes mellitus, neurodegenerative disorders, and cardiovascular injuries, in the near future. This technical report will provide a general overview of selenoproteins and their functions.

INTRODUCTION

Selenium (Se), is a vital trace element required by many living organisms. The main sources of Se are bread, cereals, eggs, meat, fish, dairy products, fruits and vegetables. It is an antioxidant and shielding the cells from damage. It is mainly found in selenocysteine (Sec) and incorporated in selenoproteins functioning in boosting immune system, reducing inflammation, decreasing cardiovascular disease and inhibiting cancer progression. Its depletion is accepted as a factor contributing to various pathological conditions, such as cardiovascular disease, neuromuscular disorders, certain cancers, male infertility, and inflammation.[1]

Se, has a very narrow range between beneficial and harmful levels. Deficiency symptoms can appear with daily intake levels below 18 µg, while toxic effects may occur when intake exceeds 400 µg.[2] Concidering cancer, plasma Se concentrations below 140 µg/L are linked to a significantly increased risk. On the other hand, levels above 400 µg/L are associated with selenosis, while concentrations exceeding 1000 µg/L indicate acute Se toxicity. The ideal baseline range for Se in plasma is considered to be between 110-135 µg/L, with the production of plasma selenoproteins reaching a plateau around 130 µg/L.[3]

Our understanding of Se's crucial role has significantly deepened since Rotruck and his team identified the first selenoprotein 50 years ago (Figure 1).[4] Though most selenoproteins serve oxidoreductase functions, its importance for immun regulation, thyroid hormon metabolism and etc, its need for proper brain function is undeniable. Studies have revealed that lacking certain selenoproteins in the brain can harm neuronal health and, may trigger neurodegeneration. Additionally, the redox balance maintained by selenoproteins may play a role in modulating neuronal functions such as neurotransmission.[5,6]

Biosynthesis and Types of Selenoproteins

To date, over 50 different selenoprotein families have been identified. The presence and types of selenoproteins can vary significantly between different species.[5] A majority of Se-containing proteins incorporate the element as the amino acid Sec. Within cells, Sec represents the predominant form of Se and is distinctive because it is encoded by the UGA codon-a codon that normally functions as a stop signal in the standard genetic code (Figure 2).[5] The human selenoproteome is encoded by 25 genes, and it is expected that many more selenoproteins will be found through genome and sequence analysis.

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One key feature common for all selenoproteins is the presence of Sec residues in their sequence. The physiological functions of selenoproteins strictly depend on the presence of Sec, and mutations of Sec to any other amino acid residue leads to enzyme inactivation.[5]

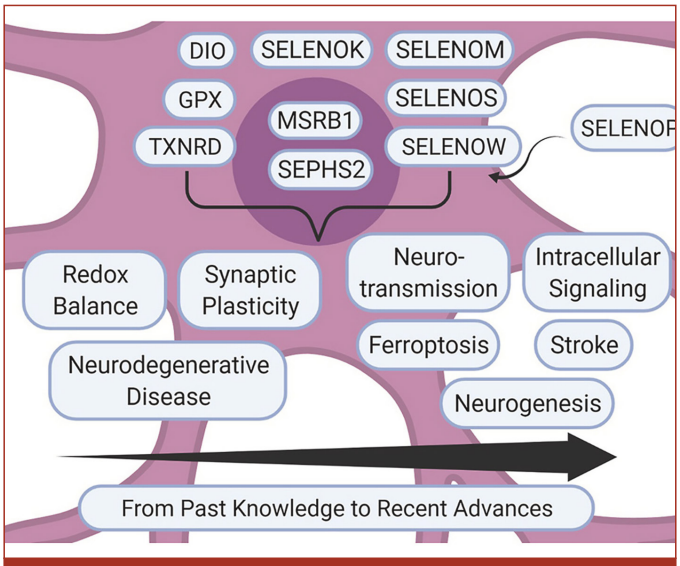

Figure 1. Selenoproteins from past to future[4]

GPX: Glutathione peroxidase, TXNRD: Thioredoxin reductase, SELENOP: Selenoprotein P

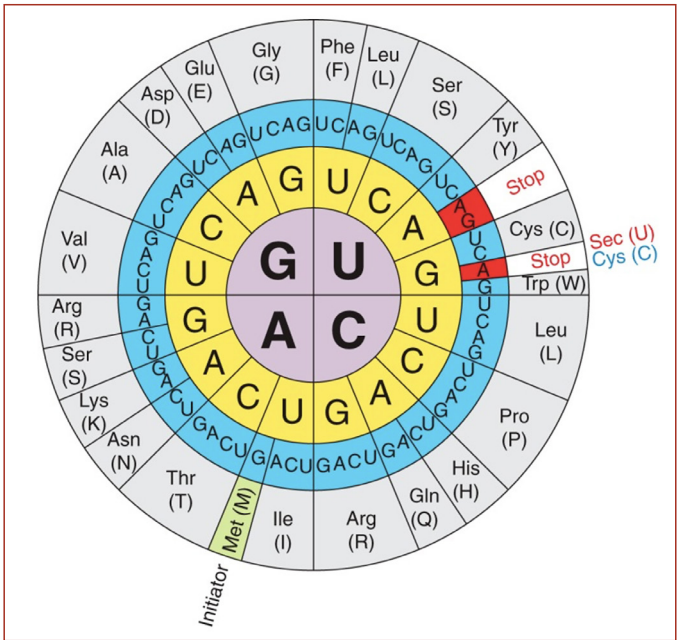

Figure 2. The genetic code illustrating the dual function of the UGA codon and that Sec is the 21st amino acid that is encoded by UGA[7]

Sec: Selenocysteine

All of the selenoproteins contain one Sec residue, only selenoprotein P (SelP) has 10 Sec residues. Selenoproteins are classified into two large groups in accordance with their Sec location. One of these two groups contains Sec in a site adjacent to the COOH terminal region of the protein, such as selenoproteins S, R, O, I, K, and thioredoxin reductases (TRXRs). The other group has Sec in the NH2-terminal region of the protein, such as H, M, N, T, V, W, F (Sep15), selenophosphate synthetase, glutathione peroxidases (GPXs), and deiodinases (DIOs).[7]

The GPXs, TRXRs and DIOs were the first selenoproteins discovered and are the most extensively studied ones. The GPXs are integral to antioxidant glutathione pathways, providing protection from reactive oxygen species (ROS), the TRXRs use NADPH for reduction of thioredoxin in cellular redox pathways and the DIOs ceave iodine-carbon bonds in the metabolism of thyroid hormones.[8]

The synthesis of selenoproteins is variably influenced by the availability of Se. Under Se-deficient conditions, the production of certain selenoproteins-such as GPX1, MsrB1, SelW, and SelH-is markedly reduced. These proteins, which are more sensitive to Se levels, are often categorized as stress-responsive selenoproteins. In contrast, another subset of selenoproteins, including TR1 and TR3, shows relatively stable expression regardless of dietary Se intake. These are typically referred to as housekeeping selenoproteins, reflecting their consistent expression to support essential cellular functions.[5]

Functions of Selenoproteins

Selenoproteins are key regulators of stress responses, metabolism, and immunity. At least 12 of the known selenoproteins are involved in immune functions and cancer mechanisms. Eleven of the selenoproteins primarily have redox-active function. These selenoproteins have emerged as central regulators of cellular antioxidant capacity and maintenance of redox homeostasis. Other 14 selenoproteins such as F, K, M, N, S, and T encoded within the human genome, have been implicated in endoplasmic reticulum (ER) homeostasis and utilize their oxidative capabilities in protein folding.[3]

The primary functions of selenoproteins include:

- Redox-active functions (antioxidant defense)

Protects endothelial cells from peroxynitrite damage.

Reduces the effect of many reactive oxygen species such as hydrogen peroxide and lipid hydroperoxide.

Protects immune cells from oxidative stress.

Reduces cytokine release.

Regulates many antioxidants.

• Thyroid hormone metabolism

• Immune regulation

• **Protein folding and quality control:** Selenoproteins localized in the ER contribute to proper protein folding and the regulation of cellular stress responses. They also help in the removal of misolded proteins.

• **Anti-inflammatory and anti-apoptotic functions:** These proteins participate in the suppression of inflammatory pathways and the inhibition of programmed cell death.

• **Regulation of energy metabolism:** Mitochondrial selenoproteins support cellular energy production and metabolic homeostasis through their roles in oxidative phosphorylation and redox regulation.

Other than, SelP and selenoprotein W (SelW), majority of selenoproteins have no known functions. SelW is a small intracellular protein, binds glutathione and function in oxidant defense. SelP is an extracellular glycoprotein and is the most common selenoprotein found in the plasma. It was shown that, patients with high SelP levels (>5.9 mg/L) had significantly lower risk for all-cause mortality and cardiovascular mortality.[9] Plasma concentration of SelP also correlates with protection against diquat liver injury, suggesting that the protein protects against oxidant injury. The disturbance in SelP cellular concentration results in pathophysiological conditions such as insulin resistance, diabetes mellitus type 2, hyperglycemia and pulmonary arterial hypertension.[10]

Selenoprotein N, is expressed in skeletal muscle, heart, lung, and placenta and it controls redox state of the intracellular calcium-release channel [ryanodine receptor (RyR)], and affects Ca^{2+} homeostasis. Its encoded by the *SEPN1* gene. Mutations in the *SEPN1* gene, causing the knockdown of selenoprotein N accompanied by recessive gene RYR1 that encodes RyR1, which are both proteins implicated in calcium homeostasis, cause severe congenital myopathies. In addition to myopathies, these mutations also lead to impaired insulin action in skeletal muscle by decreasing Akt (protein kinase B) phosphorylation and high ER stress. All these facts indicate a correlation between the decrease in glucose tolerance, insulin activity, and increased ER stress in muscles.[5]

Selenoproteins also possess a strong correlation with human cancer. Selenoproteins, enzymes that selectively include the amino acid Sec, make up major classes of antioxidant proteins critical for the protection of cancer cells to elevated ROS. Nearly all GPX and TRXR enzymes fall into this category as a catalytic Sec is essential for their activities. Selenoprotein gene polymorphisms have been linked to risk of cancer, such as; SelP is associated with the tumogenesis of colon cancer, whereas Sep15 polymorphisms may increase lung cancer risk. SelK can inhibit cell adhesion and the migration of human gastric cancer cells, besides it is critical in promoting calcium fluxes that induce melanoma progression.[11] Due to the limited research on selenoproteins, the relationship between selenoproteins and cancer has not yet been revealed. Se supplementation do not change all selenoproteins equally, the direct roles of selenoproteins need to be examined to assess whether supplementation is advisable for treatment or prevention of a specific cancers.

CONCLUSION

In conclusion, selenoproteins, including those containing the amino acid Sec, are intrinsic components of living organisms. They fulfill a broad range of physiological roles, notably functioning as antioxidants and participating in thyroid hormone metabolism. In mammals, the diverse functions of selenoproteins involved in the regulation of energy metabolism, as well as in anti-inflammatory, anti-apoptotic, and anti-ferroptotic responses, require precise spatial and temporal regulation. Innovative research on the medical applications and therapeutic potential of selenoproteins is expected to continue. In the near future, it is anticipated that selenoproteins will undoubtedly be utilized in the treatment of various pathologies, including cancer, diabetes mellitus, neurodegenerative disorders, and cardiovascular injuries.

Footnotes

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