Assosiation of serum Urea and Creatinine with other biochemical markers in multiple myeloma patients

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Abstract

Multiple Myeloma is a type of blood cancer that affects the plasma cells. Plasma cells are immune cells that normally make special proteins, called antibodies, to fight off disease. So, the present study aimed to determine some biochemical parameters among patients with multiple myeloma and healthy individuals. One hundred twenty patients with multiple myeloma and sixty healthy control were attending the National Center for Teaching Laboratories (NCFTL), Baghdad Hospital Advisory (BHA), and Baghdad Teaching Hospital. during the period from November 2021 to March 2022. Which included age, genus, drugs used, and other medical details. Multiple myeloma disease was diagnosed using symptoms, biochemical testing, x-ray, and clinical examination by specialists. Then all the biochemical test is done by Autoanalyzer. The present study found the most common symptoms are fatigue (100 %) and pain (100 %) are more common in multiple myeloma patients than other symptoms. Also the study revealed that the male patients in the age range (60- 69) and (50- 59) years are more percentage (30 %, 20 % and 36 %,16.7%) than female patients in both studied groups. The multiple myeloma disease patients with urea and creatinine above normal had a highly significant increase (p= 0.000) in the mean ± SD of urea, creatinine, total protein, and globulin (57.83±30.92 mg/dl, 2.09±1.38 mg/dl, 77.95±13.08 g/l, and 42.52±11.16 g/l) respectively. Also, patients with urea and creatinine normal had a highly significant increase (p= 0.000) in the mean ± SD of creatinine, total protein, and Globulin (0.80±0.20 mg/dl, 73.07±11.75 g/l, and 40.34±10.67 g/l) respectively compared with the healthy controls. While the highly significant decrease in the mean ± SD of S. Albumin, S. Calcium, and Hb (35.4230±3.62170 g/l, 8.16±1.31 mg/dl, 10.09±1.71 g/dl) respectively in patients with urea& creatinine above normal compare with a healthy group.

Keywords: *multiple myeloma (MM); urea, creatinine, calcium; Hemoglobin (Hb).*

P-ISSN: 2664-0562
E-ISSN:2664-0554

تقدير نسبة الكالسيوم والهيموغلوبين مع الماركرات البيوكيميائية الاخرى في مرضى المايلوما المتعددة

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الخلاصة

المايلوما المتعددة هي نوع من أنواع سرطان الدم التي تصيب خلايا البلازما. خلايا البلازما هي خلايا مناعية تصنع عادة بروتينات خاصة تسمى الأجسام المضادة لمحاربة المرض. لذلك هدفت الدراسة الحالية إلى تحديد بعض المتغيرات البيوكيميائية بين مرضى المايلوما المتعددة والأفراد الأصحاء. مائة وعشرون مريضا يعانون من الورم النخاعي المتعدد وستين من الاشخاص الاصحاء تم اخذ العينات من المركز الوطني للمختبرات التعليمية واستشارية مستشفى بغداد ومستشفى بغداد التعليمي خلال الفترة من نوفمبر 2021 إلى مارس 2022. والتي تضمنت العمر والجنس والأدوية المستخدمة وتفاصيل طبية أخرى. تم تشخيص مرض المايلوما المتعددة باستخدام الاختبارات البيوكيميائية, الأعراض, الأشعة السينية والفحص السريري من قبل متخصصين. ثم يتم إجراء جميع الاختبارات البيوكيميائية بواسطة أجهزة تحليل اوتوميتيد (ذاتية) وجدت الدراسة الحالية أن الأعراض الأكثر شيوعًا هي التعب (100٪) والألم (100٪) أكثر شيوعًا لدى مرضى المايلوما المتعددة من الأعراض الأخرى. كما أوضحت الدراسة أن المرضى الذكور في الفئة العمرية (60-69) و (50-59) سنة أكثر نسبة (30٪ ، 20٪ ، 36٪ ، 16.7٪) من الإناث في المجموعتين المدروستين. كان لدى مرضى المايلوما المتعددة الذين يعانون من اليوريا والكرياتنين فوق المعدل الطبيعي زيادة كبيرة في المتوسط = الانحراف المعياري لليوريا والكرياتينين والبروتين الكلي والجلوبيولين (57.83 ± 30.92 مجم / ديسيلتر 2.09 1.38 مجم / ديسيلتر ، 77.95 13.08 جم / لتر و 42.52 + 11.16 جم 1) على التوالي. أيضًا ، كان لدى المرضى الذين يعانون من اليوريا والكرياتينين الطبيعي زيادة كبيرة للغاية (p = 0.000) في متوسط SD ± للكرياتينين والبروتين الكلي والجلوبيولين (0.80 0.20 مجم / ديسيلتر ، 73.07 = 11.75 جم 1 ، 40.34 = 10.67 جم / 1) مقارنة بالضوابط الصحية.بينما كان الانخفاض معنويا للغاية في متوسط لكلا من الالبومين والكالسيوم والهيموغلوبين في المرضى الذين يعانون من ارتفاع اليوريا والكرياتنين مقارنة مع مجموعة اصحاء.

الكلمات المفتاحية: *المايلوما المتعددة ، اليوريا، الكرياتنين ، الكالسيوم، الهيموغلوبين(خضاب الدم).*

Introduction

Multiple myeloma (MM) is a type of plasma cell malignancy that is associated with a high mortality rate and severe renal impairment (RI). Kidney injury can restrict treatment options and result in poor outcomes, yet it is curable in some cases. When determining the prognosis of patients with multiple myeloma, this test comes in handy. Diagnosis of renal tubular disease [1]. In high-income countries, multiple myeloma is the second most common hematological malignancy, accounting for 1% of all cancers [2]. The clinical and biochemical heterogeneities of this malignancy cause variable responses to therapy and prognosis [3]. Two of the differentiating markers of MM are renal impairment and a serum creatinine > 2.0 mg/dl connected to plasma cell dyscrasia. MM is the most common monoclonal gammopathy that causes renal damage [3] . Due to population expansion, an ageing world population, and rising age-specific incidence rates, the global incidence of multiple

P-ISSN: 2664-0562
E-ISSN:2664-0554

myeloma grew by 126 percent from 1990 to 2016[2]. Multiple myeloma is a malignant tumour that develops out of control when plasma cells become cancerous. Monoclonal immunoglobulin, monoclonal protein (M protein), M-spike, or paraprotein are all names for an aberrant protein (antibody) produced by plasma cells [4]. The experts concluded that there is little evidence linking atomic bomb exposure to an increased risk of multiple myeloma. Many populations have been examined for occupational exposures. A major meta-analysis of data from farmers in the central United States found a relative risk of 1.38, however it was unclear if this elevated risk was due to pesticide exposure, solvent exposure, infectious agent exposure, or other reasons. Hair colour exposure has been linked to an increased incidence of multiple myeloma. Exposure to benzene and petroleum products has also been linked to the development of multiple myeloma, but there is little evidence to substantiate a causative relationship [5]. The age-standardized incidence in the Western world has been estimated to be around 5 cases per 100,000[6]. A person in Europe has a 0.31 percent chance of developing multiple myeloma during his or her lifetime. This indicates that every year in Europe, 4 to 6 cases will be diagnosed out of every 100,000 people. Women have a lower incidence. The median age at the time of diagnosis is 72 years old. Afro-Americans have a higher rate of infection, while Asians have a lower rate [7].

Researchers discovered that patients with plasma cell tumours have significant abnormalities in other bone marrow cells, which may induce excessive plasma cell proliferation as well. Dendritic cells in the bone marrow release a hormone called interleukin-6 (IL-6) that stimulates the growth of normal plasma cells. Excessive IL-6 production by these cells appears to be a key element in plasma cell tumour growth [8]. The iron-containing oxygen transporter protein haemoglobin (Hb) is located inside RBC and gives blood its red colour. The heme group and globin proteins are found in Hb. Heme group contains iron and has the ability to bind to oxygen; oxygen is bound to Hb and delivered from the lungs to the body via blood vessels, where it is freed to burn nutrition for energy while carbon dioxide is collected and returned to the respiratory organs [9]. Blood chemistry tests are used to determine the quantities of various substances in the blood. The findings are utilised to determine the impact of MM or treatment on various body organs (such as the kidney). Test for urea: Urea is a waste product of protein breakdown in the liver that the kidneys filter out of the circulation and into the urine. The urea test is used to determine how well your kidneys are working. Creatinine: Creatinine is a waste product produced by muscles that the kidneys filter out of the bloodstream and excrete in the urine. Creatinine will build up in the circulation if the kidneys are damaged and unable to filter it out, as seen by high creatinine levels on a blood test. Calcium, on the other hand, is a mineral found in many bodily tissues, particularly the bones.

P-ISSN: 2664-0562
E-ISSN:2664-0554

Calcium is also essential for muscle, neurone, and cardiac function to be proper. High levels in a blood test can indicate kidney and/or bone damage [10]. Hypercalcemia is a typical symptom of multiple myeloma patients. Smoldering myeloma and monoclonal gammopathies of unknown importance are distinguished from active, symptomatic multiple myeloma by the four diagnostic "CRAB" criteria (calcium elevation, renal insufficiency, anaemia, and bone disease). The destruction of bone in multiple myeloma leads to the release of calcium into the bloodstream, resulting in hypercalcemia. Two human skeletons with this bony lesion pattern — both males, between the ages of 40 and 60 years at death [11]. If proper treatment is not offered right away, this might become a major problem. [12].

Materials & Methods

Patients & control

The current examination took place at three main medical facilities in Baghdad between November 2021 and March 2022: the National Center For Teaching Laboratories (NCFTL), Baghdad Hospital Advisory (BHA), and Baghdad Teaching Hospital. Each patient filled out a unique questionnaire with descriptive information. The questionnaire asked for information such as age, genus, drugs used, and other medical details. Multiple myeloma disease was diagnosed using symptoms, biochemical testing, x-ray, and clinical examination by specialists. This study excluded people with chronic illnesses and patients with Multiple Myeloma who had been on medications for a long time. Patients with Multiple Myeloma were divided into two groups: those with normal urea and creatinine concentrations, and those with abnormal urea and creatinine concentrations, as well as sixty control groups made up of medical staff and patient's families. Patients were selected based on their gender and age. There are (40) males and (20) females in each group, with ages ranging from 40 to 80.

Biological Samples

Using disposable syringes, 10 ml of blood was drawn from each participant and divided into two tubes: 6 ml of serum for biochemical tests (B. urea, S. creatinine, S. calcium, S. Total protein, serum albumin, S. globulin, and calcium) by Autoanalyzer. EDTA tube, which is used to evaluate Hb levels, is also present in 2ml of blood deposited in tubes.

P-ISSN: 2664-0562
E-ISSN:2664-0554

Statistical analysis

The data was reviewed, coded, and analyzed using the "Statistical Package of Social Science (SPSS) version 26.0."

1-For data visualization, use: - Data in a tabular format (Complex frequency distribution table).

- Mathematical presentation method (Mean and Stander Deviation).

2-Use the following for data analysis:

- Independent Samples T-test

- A paired-samples T-test.

The significance (p-value) was compared in each test as follows:

non-statistically significant Garter P-Value >0.05 (P>0.05) (NS).

P0.05 or below was considered statistically significant (S).

P-values of 0.01 or less (P0.01) were very significant statistically (HS).

Results

According to the characteristic of multiple myeloma patients, it was clear from a table (1): A highly significant differences (P=0.000) in both studied groups when divided into two groups, the first group of patients with urea and creatinine normal that there were show fatigue (100%) and pain (100%) are more common in multiple myeloma patients than other symptoms includes weakness (93.3%), nausea (73.3%), vomiting (40%) and swelling (36.7%). In addition, a drug was used in this group of patients (96.7%). The second group of patients with urea and creatinine above normal that there were show fatigue (100%) and pain (100%) are more common in multiple myeloma patients. While other symptoms include weakness (93.3%), nausea (86.7%), vomiting (30%), and swelling (60%). Thus, the drug used in this group of patients (90%).

P-ISSN: 2664-0562
E-ISSN:2664-0554

Table (1): Distribution of Patient groups according to the symptoms & Drugs used.

	Patients groups				P-Value
	Patient with urea & creatinine normal (n=60)		Patients with urea& creatinine above normal(n=60)		
	YES (n=40)	NO (n=20)	YES (n=40)	NO (n=20)	
Fatigue	60(100%)	0(0.0%)	60(100%)	0(0.0%)	P=.000 (HS)
Weakness	56(93.3%)	4(6.7%)	56(93.3%)	4(6.7%)	P=.000 (HS
Vomiting	24(40%)	36(60%)	18(30%)	42(70%)	P=.000 (HS)
Swelling	22(36.7%)	38(63.3%)	36(60%)	24(40%)	P=.000 (HS)
Nausea	44(73.3%)	16(26.7%)	52(86.7%)	8(13.3%)	P=.000 (HS)
Pain	60(100%)	0(0.0%)	60(100%)	0(0.0%)	P=.000 (HS
Drugs use	58(96.7%)	2(3.3%)	54(90%)	6(10%)	P=.000 (HS

The baseline characteristics of the studied groups according to the age and sex with the comparison of significance were observed in table (2). This table revealed that the male patients in the age range (60- 69) and (50-59) years are more percentage (30%, 20% and 36%, 16.7%) than female patients in all studied groups with a significant difference in gender of the healthy group (p= 0.00) and no significant difference in a gender of patients with urea& creatinine above normal groups (P= 0.433). In addition, a significant difference in gender between patients with urea& creatinine with normal groups (P=0.017).

Table (2): Distribution of Studied groups according to Age groups(Years) and Sex.

Age groups (Years)	Studied groups					
	Healthy control (n=60)		Patient with urea & creatinine normal (n=60)		Patients with urea& creatinine above normal(n=60)	
	Sex		Sex		Sex	
	Male (n=40)	Female (n=20)	Male (n=40)	Female (n=20)	Male (n=40)	Female (n=20)
(40-49)	6 (10.0%)	6 (10.0%)	8 (13.3%)	2 (3.3%)	0 (0.0%)	0 (0.0%)
(50-59)	18 (30.0%)	2 (3.3%)	12 (20.0%)	8 (13.3%)	10 (16.7%)	8 (13.3%)
(60-69)	10 (16.7%)	12 (20.0%)	18 (30.0%)	4 (6.7%)	22 (36.7%)	10 (16.7%)
(70-79)	6 (10.0%)	0 (0.0%)	2 (3.3%)	6 (10.0%)	8 (13.3%)	2 (3.3%)
P-Value	P=.000 (HS)		P=.017 (S)		P=.433 (NS)	

(HS)= highly significant, (S)= significant

P-ISSN: 2664-0562
E-ISSN:2664-0554

Table (3) shows a comparison in urea, creatinine, total protein, albumin, globulin, calcium and Hb between the studies groups which include healthy (control), patients with urea and creatinine normal, and patients with urea and creatinine above normal. The multiple myeloma disease patients with urea and creatinine above normal had a highly significant increase (p= 0.000) in the mean ± SD of urea, creatinine, total protein and globulin (57.83±30.92 mg/dl, 2.09±1.38 mg/dl, 77.95±13.08 g/l and 42.52±11.16 g/l) respectively. In addition, patients with urea and creatinine normal had a highly significant increase (p= 0.000) in the mean ± SD of creatinine, total protein, and Globulin (0.80±0.20 mg/dl, 73.07±11.75 g/l, and 40.34±10.67 g/l) respectively compared with the healthy controls (0.67±0.15624 mg/dl, 66.63±4.66 g/l, 26.77±3.25 g/l, 14.35±7.49, 165.80±90.77) respectively. While the highly significant decrease in the mean ± SD of S. Albumin, S. Calcium, and Hb (35.4230±3.62170 g/l, 8.16±1.31 mg/dl, 10.09±1.71 g/dl) respectively in Patients with urea& creatinine above normal and the mean ± SD of S. Albumin, S. Calcium and Hb (32.79±5.95 g/l, 8.81±0.87 mg/dl, 11.48±2.27 g/dl) respectively in Patients with urea & creatinine normal compare with a healthy group (40.31±4.64 g/l, 9.69±0.47 mg/dl, 13.11±0.96 g/dl) respectively. While non-significant in the mean ± SD of S. urea (p=0.243) (29.82±11.53 mg/dl) in the Patients with urea& creatinine normal.

Table (3): Compare the biochemical parameters between studied groups.

Parameters	Mean ±Std.		
	Patients with urea & creatinine normal	**Healthy control**	**Patients with urea& creatinine above normal**
S. urea(mg/dl)	29.82±11.53	32.00±8.57	57.83±30.92
	P= .243 (NS)		P=.000 (HS)
S. Creatinine(mg/dl)	0.80±0.20	0.67±0.15624	2.09±1.38
	P=.000 (HS)		P=.000 (HS)
S. Total protein (g/l)	73.07±11.75	66.63±4.66	77.95±13.08
	P=.000 (HS)		P=.000 (HS)
S. Albumin (g/l)	32.79±5.95	40.31±4.64	35.4230±3.62170
	P=.000 (HS)		P=.000 (HS)
S. Globulin (g/L)	40.34±10.67	26.77±3.25	42.52±11.16
	P=.000 (HS)		P=.000 (HS)
S. Calcium (mg/dl)	8.81±0.87	9.69±0.47	8.16±1.31
	P=.000 (HS)		P=.000 (HS)
Hb(g/dl)	11.48±2.27	13.11±0.96	10.09±1.71
	P=.000 (HS)		**P=.000 (HS)**

P-ISSN: 2664-0562
E-ISSN:2664-0554

Discussion

The present study observed the same results as the studies were done by the Rajkumar, 2016 and Multiple Myeloma Research Foundation Accessed April 5, 2021, which found that the most common symptoms in multiple myeloma patients are fatigue, pain, and weakness are usually associated with anemia in multiple myeloma[13,14]. Also, the study found that the male patients more than the female patients which agrees with another study done by Carrero *et al.*, 2018 which found that the kidney function declines faster in men than women, possibly owing to unhealthier lifestyles in men and the protective effects of estrogens or the damaging effects of testosterone[19]. In addition, the current study agrees with other studies done by Canadian Cancer Statistics 2009, Alexander DD,2007 which found that a higher percentage with multiple myeloma disease over the age of 60 years [15]. In which the incidence of acute kidney injury in elderly persons can be potentially attributed to the following: A) comorbidities that accumulate with age may facilitate acute kidney injury (e.g., renovascular disease, congestive heart failure); B) comorbidities may necessitate procedures, drugs, or surgery that function as kidney stressors and nephrotoxins; C) the kidney undergoes age-dependent structural and functional alterations over time. Also, the result of the latter is a reduced glomerular filtration rate at baseline and a diminished kidney reserve in the setting of pathophysiological challenges, lending elderly patients very vulnerable to acute stress and more likely to develop clinically relevant acute kidney injury similar to prevalence [16].

The finding of this study agree with Andronesi,2019 who found that kidney involvement is a prominent feature of multiple myeloma and is mainly due to high-tumor burden with development of myeloma cast nephropathy, but also because of hypercalcemia and tumor lysis syndrome[17]. Thus, total protein and globulin were increased in each group of patients due to the damage of the kidney [17]. The study of Salman, Salaha and Abass, 2020 who show the decrease in albumin and calcium because to the bone disorder is the most common complication in the multiple myeloma, the damage that occurs in the bone result from stimulation of osteoclast formation and activation that occurs in the area of the bone that is closed to myeloma cell. Besides, to increase the bone resorption, there is a decrease in bone formation have been reported and this attributed to the suppression effect of myeloma cell on osteoblast cell and so inhibit bone formation[18] . Finally, decrease in Hb that happen due to the kidneys when damaged, they produce less erythropoietin (EPO), a hormone that signals bone marrow—the spongy tissue inside most of bones—to make red blood cells with less EPO, body makes fewer red blood cells, and less oxygen is delivered to organs and tissues [7].

P-ISSN: 2664-0562
E-ISSN:2664-0554

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P-ISSN: 2664-0562

E-ISSN:2664-0554