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Original article

Vitamin D deficiency as a risk factor for urinary tract infection in women at reproductive age

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ABSTRACT

Vitamin D deficiency is a pandemic problem and an ever-increasing issue in human nutrition and health. Vitamin D (serum 25-hydroxyvitamin D) deficiency causes many health problems such as autoimmune diseases, Crohn's disease, diabetes, inflammation, asthma, hypertension, and cancer. Vitamin D3 (cholecalciferol) deficiency has been documented as a persistent problem among adults, children, and elderly persons in most of the countries. Our main objective of this study was to determine the hypothesis that the vitamin D deficiency among women can lead to them developing frequent urinary tract infections. Vitamin D has a potential role in immune regulation and it prevents infections especially urinary tract infections (UTI). Therefore it has positive regulatory role in both acute and recurrent infections especially in women of reproductive ages. As women at this age group have specific differences in their urinary tract and the reproductive organ anatomy, make them more prone for micro-organisms' invasion, The present study was carried out to ascertain certain relation between serum 25-hydroxyvitamin D levels and UTI in women while contemplating the significance of knowing the risk factors associated with UTI and also finding ways to avoid serious complications. 75 women with (case group) UTI were differentiated with 35 healthy with no UTI (control group) and 40 women with UTI and their serum 25-hydroxyvitamin D levels were checked in a case control study. The women were between at 17–52 years of age. Using ELISA, Serum 25-hydroxyvitamin D levels were measured. Analysis and comparison of the results were done among the two groups. Vitamin D mean levels in the case group was considerably lower when in comparison with the control group (11.09 ± 7.571 ng/mL vs. 24.08 ± 11.95 ng/mL, $P < 0.001$).

1. Introduction

Vitamin D deficiency is a pandemic. One-third of the worldwide population suffers from vitamin D hypovitaminosis due to inadequate exposure to sunlight (Adams et al., 2007; Holick, 2004). It is estimated that In Africa and Asia, more than 80% of the people are prone to vitamin D deficiency (Keflie et al., 2015; Ritu and Gupta, 2014). Serum 25-hydroxyvitamin D deficiency can play role in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease (Amdekar et al., 2011; Holick, 2004).

Increasing intestinal absorption of phosphate, magnesium and calcium multiple other biological effects are the responsibility of vitamin D, which is a group of fat-soluble secosteroids (Bakacak et al., 2015). Vitamin D2 and D3 which are otherwise known as ergocalciferol and cholecalciferol are the most important in humans. Both can be found in food or as supplements (Holick, 2006). By measuring the blood plasma concentration of 25-hydroxyvitamin D, vitamin D deficiency can be diagnosed (Deficiency being less than 10 ng/ml, Insufficient: 10–29 ng/ml, Sufficient: 30–70 ng/ml and Potential intoxication: more than 70) (Hewison, 2012; Holick et al., 2011; Institute of Medicine, 2010). There are several health consequences associated with the vitamin

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D deficiency including bone problems (as osteoporosis) (Winzberg and Jones, 2013) autoimmune diseases (as Pre-eclampsia) and infections (Hertting et al., 2010; Hewison et al., 2001). Recent research shows that the risk of vitamin D deficiency includes many bacterial infections for instance both respiratory and urinary tract infections (Laaksi et al., 2007; Lane and Takhar, 2011). Now studies focus on the non-classical functions of vitamin D, i.e. other than its effects on bone metabolism, these include effect on immune system (both the innate and adaptive) such as cell proliferation and differentiation as well as immunologic effects resulting incapability to maintain tolerance and promotion of protective immunity (Keflie et al., 2019). In one hand the innate immune system enhanced by vitamin D via inducing an antimicrobial peptide called cathelicidin that assists in infection prevention. On the other hand, by the production of cytokines from both B and T Cells and by suppressing the inflammation, vitamin D modulates the adaptive immune system (Holick, 2007).

Urinary tract infection (UTI) is a severe health disease with high complication because it is related to antibiotic resistance and threatening to health throughout lifetime (Ananthanarayan and Paniker, 2013). According to the World Health Organization (WHO), urinary diseases cause death of almost 85,000 people in the world per year (Flores-Mireles et al., 2015). In a hospitalized population, one of the prevalent contracted bacterial infection is Urinary tract infection (UTI) and especially in 11% of all women of ages between 18 and 24 years (Arellano, 2011) and nearly 1 in 3 women will have had at least 1 episode of UTI requiring antimicrobial therapy during their reproductive age (Ananthanarayan and Paniker, 2013). In this infection, most parts of the urinary system like urethra, kidneys, bladder and ureters gets affected. The urethra and bladder, parts of the lower part of the urinary tract are involved in most of the infections (Salvatore et al., 2011). In comparison with men, women are often found to be at a higher risk of UTI development. This is because of anatomical difference of female Urinary tract and changes that happen at it, for example at sexual intercourse and at child birth (Salvatore et al., 2011).

Burning sensation while urinating and severe pain are the main symptoms of a lower urinary tract infections. Additionally, felling of needing to urinate while the bladder being empty and recurrent urination are indications (Alqasim et al., 2019). These symptoms could be mild to severe. Kidney infection symptoms also include vomiting, fever, nausea and flank pain (Alqasim et al., 2019; Jawetz, 2004). *Escherichia coli* generally considered to be the causative agent in the case of Urinary tract infection (in about 80–85%) and *Staphylococus saprophyticus* (in about 5–10%), *Klebsiella, Proteus, Pseudomonas* and *Enterobacter* are other bacteria causing of UTI (Al-Naqshbandi et al., 2019; Hooton, 2001). Rarely viral or fungal infections causes UTI (Arellano, 2011) although these causative agents are not common and mostly infect individuals with urinary catheterization or with structural abnormalities in their urinary tract (Chu and Lowder, 2018).

Mostly Women contract UTI while compared to men for many reasons, including anatomical differences (shorter urethra thus easier bacterial ascend), sexual activity and the state of menopause (hypo-estrogenic state that also happens during puerperium). Other factors include suppressed immunity like diabetes and sometime with a recent urinary procedure (Ananthanarayan and Paniker, 2013).

The urinary tract is frequently attacked by many pathogens; therefore rapid defense mechanisms are required. Bladder epithelial cells secrete and express a human antimicrobial peptide names as cathelicidin which protects the lower urinary tract. Vitamin D induces cathelicidin of the urinary bladder epithelium. As it provide protection against both gram negative and positive bacteria, we can conclude that this compound has a broad spectrum of action. Moreover it also show actions against some protozoa and fungi. Considering these viewpoints, this study's main purpose was to determine the relation between serum vitamin D3 deficiency and UTI in women at reproductive age.

2. Material and methods

2.1. Study design

Case-control (retrospective observational) study was designed and conducted at a tertiary Hospital (Rizgary Teaching Hospital), in Erbil city. We have had collected data form 110 women who visited day clinic. Those selected women were at reproductive age between (17–52 years) (Winzberg and Jones, 2013) divided between two groups, those who had symptoms of UTI and account for 75cases (patients) and those who do not, they were 35cases (controls). We send them all for investigations include general urine examination (by clean catch mid-stream urine sample), urine for culture, complete blood count and vitamin D. The data were collected over a period of 5 months.

2.2. Specimen collection and bacterial identification

Laboratory diagnosis for urinary tract infections are include taking clean catch mid-stream urine from each patient collected into a 20 mL calibrated sterile crew-capped universal container which were distributed to the patients. The specimens were labeled, transported to the laboratory for both general urine examination and culturing. The pathogens were identified and isolated by conventional techniques (McCartney and, Mackie 14th edition). A urine culture is positive when 10^5 CFU/mL (colony forming unit) of a single pathogen is found in mid-stream urine. Standard loop semi-quantitative technique of inoculation had been used to determine the pathogenic microorganism in significant numbers and un-centrifuged urine in known volume by spread plate method was used. Blood agar and McConkey agar plate were used for isolation of causative organism and incubated for 24–48 h at 37 °C (Kakoo and Kheder, 2016; Akmal et al., 2014). All media were examined aftertimes of incubation, if no growth occurs they were incubated for another 24 h before regarded as negative whereas few samples were identified with VITEK 2 compact system protocols by using these kits: VITEK®2 GN Reference 21341, VITEK®2 GP Reference 21342, VITEK®2 AST-GN69 Reference 413400, VITEK®2 AST-P580 Reference 22233, and VITEK®2 AST-ST01 Reference 410028 (Al-Naqshbandi et al., 2019).

2.3. Blood samples

Venous blood specimens were collected from both cases and controls group and were determined for vitamin D3 test (done by commercial kit Roche Diagnostic GmbH, Vitamin D total), therefore serum 25(O) D levels analysis were done by following manufacturer's protocol Levels of 25(OH) D and categorized as deficient (<10 ng/mL) insufficient (10–29) and sufficient (30–70 ng/mL) (Holick et al., 2011). Under sterile conditions, in vacutainer tubes, blood samples are taken from the participants of this study. Separation of the serum was done by centrifugation of the obtained blood sample. And the serum was then loaded to vitamin D kit Roche E411 Analyzer. From each patient, 1 mL of the serum was shifted into designated tubes, before getting loaded in to the analyzer. Blood creatinine and urea were measured using commercially available kits from Roche diagnostics using manufacturer's instruction and total blood count was measured using medonic hematology analyzer.

2.4. Ethics statement

Above study was approved by the ethics committee of the Rizgary Teaching Hospital in Erbil city, Iraq. Research methodology in simple language was provide to all the patients. The participants below the age of 18 were added in the study after their guardians' consent. We choose women at reproductive age for this study for few reasons include (women are more prone to UTI than men because of anatomy difference between the two, also not children because of same reason and other factor like ureteric reflux, not pregnant women because of difference in immune response as hypo-or hyper immune response) (Keflie et al., 2019). Furthermore, women with history of recurrent urinary infection also included which make few cases the study. While patients who are immuno-compromised for whatever reason for example cancer, renal failure and organ transplants, were excluded from the study.

2.5. Statistical analysis

The research results were analyzed using GraphPad Prism 8.0 software. An independent *t*-test and chi-square test were used for. At P value < 0.001 and P < 0.01 respectively which considered to be statistically significant.

3. Results:

3.1. Urine analysis in patients

When checking indicators of infection, while evaluating urine analysis, there are several factors to consider. The presence of bacteria per high power field is the most common indicator of bacterial infection. Although some amounts of bacteria in urine may be present for any patient with symptoms, according to the definition, 5+ is considered as the standard for bacteriuria. Sometimes 2+ is also considered positive in some selective populations which are hospitalized and catheterized patients (Alqasim et al., 2019) The bacterial invasion determined by general urine examination and culturing (urinalysis) revealed that out of 75 urine specimens collected from patients (case group) complaining of signs and symptoms of UTIs, Fifty two samples (69.33%) were positive for bacterial infection whereas 30.66% negative. From positive cultures different bacterial type isolated, most cases were due to *Escherichia coli* (Figs. 1 and 2).

3.2. Lower amount of vitamin D in patients

After kidney function tests and the blood analysis, we checked the amount of Vitamin D in the blood samples of the patient, the main focus of this study. Serum 25(OH) D levels was analyzed from the patient group and compared to the control samples. Commercially available vitamin D analysis Kit was used to ascertain the amount of 25(OH) D in the serum of the patients as well as from the control group. Serum sample was analyzed from 110 patients and control, we found that there was a significantly lower amount of Vitamin D ($p < 0.001$) in the serum of the patients in comparison to the control group (Fig. 3).

3.3. Patients with lower amount of blood vitamin D showed higher microbial load in urine sample

We tried to examine if there was any correlation between the deficiency of vitamin D and severity of the urinary tract infection in the analyzed patient group. As it can be seen from the data in the (Tables 1 and 2) there were significantly higher number of bacteria present in the patients' urine having vitamin D deficiency. The highest number of bacteria that was found is in the urine sample of the vitamin D deficient patient.

3.4. Kidney function was normal for the analyzed patient group

Kidney function in the patients were checked by blood urea and creatinine quantity (Table 2). The analysis showed that the blood urea and creatinine levels are in the normal range among both the control and patients' sample (Fig. 4). This indicates that in both the cases kidneys were functioning properly.

3.5. Blood hemoglobin and WBC count

We also analyzed the blood samples from the patients and compare the total hemoglobin and white blood cell (WBC) count with the control samples. As we can see from the graph in (Fig. 4) the patients did not show any lower hemoglobin count and no significant abnormality in WBC count.

4. Discussion

In this case-control study, we could conclude from the results, that urinary tract infections in women at reproductive age can be linked to the deficiency of vitamin D. In some studies, they even found credible evidence between vitamin D deficiencies with recurrent urinary tract infection (Nseir et al., 2013).

To begin with the immune system both innate and adaptive systems need vitamin D for better functioning and responding to infection and inflammation (Winzberg and Jones, 2013). As we clarify before how the immune system needs vitamin D in activation of white blood cells and increase the infected cell clearance by interleukins and cytokines, also cathelicidin is stimulated and activated by vitamin D (Keflie et al., 2019). These immune effects are crucial key factor that explain the search for vitamin D deficiency among patients with symptoms of urinary tract infection. Our clean-catch mid-stream models include clinically intuitive items. Most of the bacterial isolates were gram-negative representing 57.14%, since the outer membrane proteins, that are present in some gram-negative bacteria are known to have crucial roles in pathogenesis and adaptation in host cells as well as in antibiotic resistance (Osman, 2019) while gram-positive bacteria were 42.85%, they were mostly isolated from pure culture which form 94.23%. *Escherichia coli* was among the most predominate pathogenic bacteria isolated with a rate of 34.69% of UTI cases. *Escherichia coli* (*E. coli*) is reported to be the key cause of UTIs, and the uropathogenic *E. coli*, a subset of extraintestinal pathogenic *E. coli* the group is associated with causing more than 80% of all UTIs (Salvatore et al., 2011) then *Staphylococcus saprophyticus* to form about 14%, followed by *Staphylococcus haemolyticus* and *proteusmirabilis* which represent 10% while *Enterococcus fecalis*was 8.1% followed by *Klebsiella pneumonia* 6.12% whereas both *streptococcus agalactie* and *Staphylococcus intermedius* was 4.08% and a single case of *morganella morganii* as shown in (Fig. 2). These findings somewhat similar with other researches (Hooton, 2001). According to our cultural results, there is a clear correlation between the severity of deficiency of this vitamin and positive culture for bacteria and microbes the more deficient the patient in vitamin D level the more occurrence of bacterial UTI and mixed bacterial positive culture, Indicating vitamin D as a risk factor for UTI as shown in (Table 1).

The previously mentioned cathelicidin (a group of propeptide have antimicrobial effect) which is induced by vitamin D, this is how we link between vitamin D and antimicrobial action. Although that effect of this vitamin is applied to both men and women, urinary tract infections is more common in women because of many

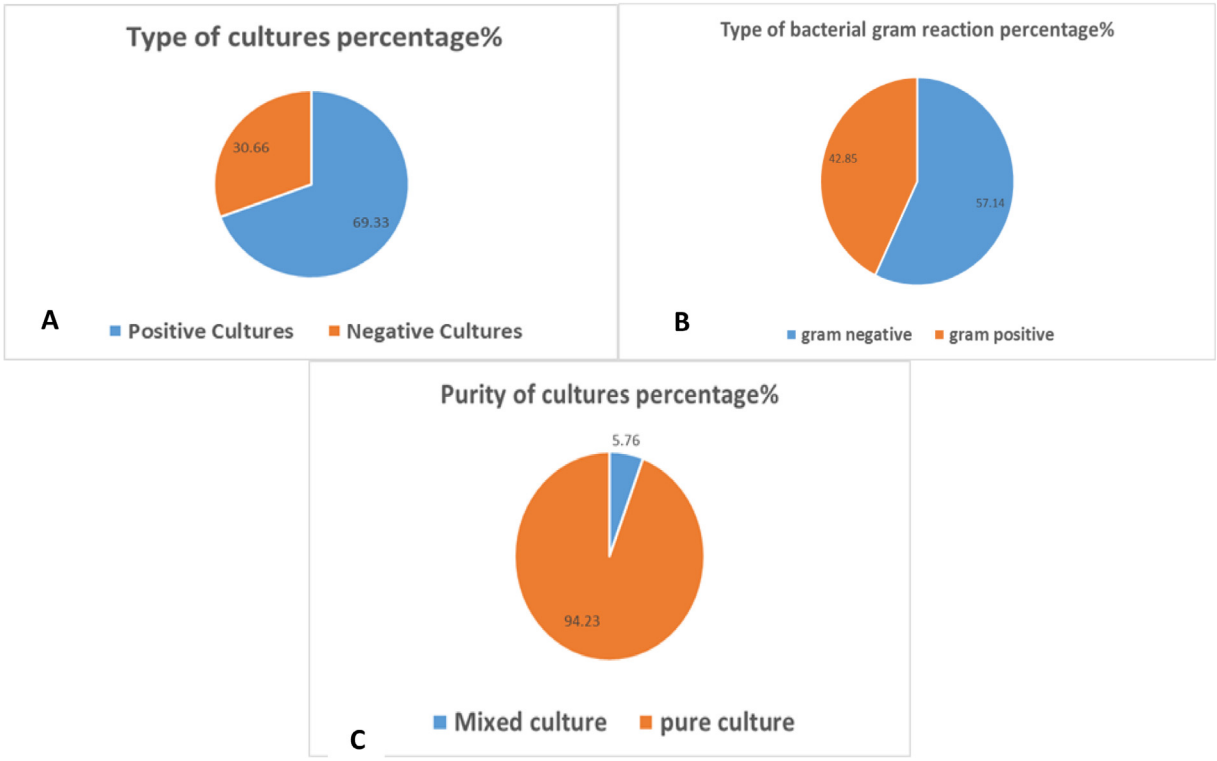

Fig. 1. Percentage of positive (A) and negative cultures (B), and purity of bacterial cultures (C) including gram positive and gram negative bacteria isolated from the patient group.

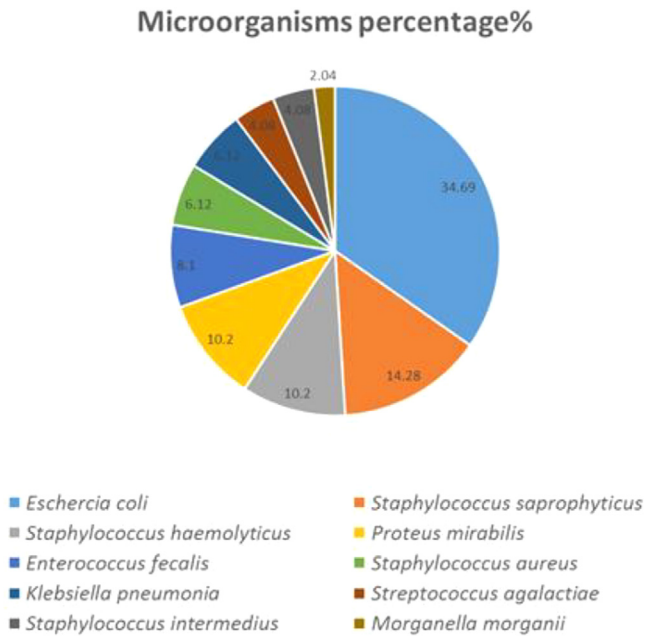

Fig. 2. Percentage distribution of bacterial isolates in patient group.

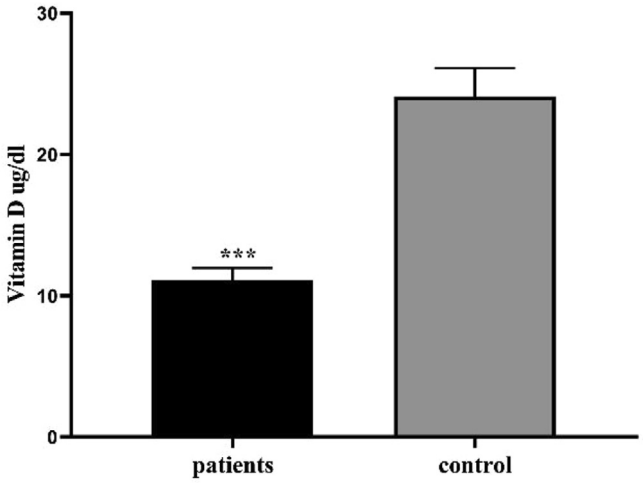

Fig. 3. Analysis of vitamin D showed significantly lower amount in the (case) patient group compared to control group.

Table 1
Correlation of vitamin D deficiency and positive bacterial cultures.

Chi-square, df	X2	P Value
Vitamin D Deficiency and Positive Cultures	10.03	0.01

factors includes, anatomical predisposition, close approximation of urethra and vagina and sexually active life during the reproductive ages (Lane and Takhar, 2011).

Furthermore, our area Middle East known has a higher rate of vitamin D deficiency, besides to less exposure to sunlight because of hot weather and veil, all these factors make this study more interesting, as from the results we found a clear link of this vitamin deficiency and infections, especially urinary tract (Hewison, 2012).

In other case-control studies, Nseir et al. (2013) and Hooton (2001) both show about 2–3 folds rise in infections including urinary tract with vitamin D deficiency, which is almost similar to our results that is 2 fold rise in the incidence of urinary tract infection with vitamin D deficiency (Tables 1 and 2).

Table 2
Correlation of vitamin D, Hemoglobin, WBC, serum creatinine and urea in both patients and controls.

Treatment	Control M ± SD	Patient M ± SD	P value
Vitamin D	24.08 ± 11.95	11.09 ± 7.571	P < 0.p001
Hemoglobin	12.48 ± 1.272	11.95 ± 1.468	N.S
WBC	7.577 ± 1.763	7.194 ± 1.874	N.S
Serum Creatinine	0.6100 ± 0.1796	0.5789 ± 0.1957	N.S
Serum Urea	23.81 ± 7.509	25.46 ± 7.657	N.S

*N.S P > 0.05, * P < 0.05 Significant, ** P < 0.01 High Significant, *** P < 0.001 Very High Significant.

Kidneys play an important role in making vitamin D useful to the body. In chronic kidney disease it has been found that vitamin D levels is below the normal range, sometimes even severely low levels. This can occur because injury in kidneys make them less able to convert vitamin D into its active form (Van Etten and Mathieu, 2005). So before went forward to check the vitamin D deficiency and vaginal microflora analysis we analyzed the kidney function in the patients by checking the blood urea and creatinine quantity (Fig. 4). The analysis showed that the blood urea and creatinine levels are in the normal range among both the control and patients' sample. This indicates that in both the cases kidneys were functioning properly and we could eliminate the fact that the vitamin D deficiency among the patients was not related to kidney malfunction or injury.

WBC count from all the patients found that the total WBC count was also in the normal range among most of the patients compare to the normalized group which indicated that the patients group analyzed for the study did not have any serious blood infection.

One of the most important statement was the recurrent cases of the urinary tract infection was not separately studied, as we took both recurrent and acute cases of urinary tract infection, because of poor patient-Hospital communication\referral from primary health care (Hooton, 2001). Another difference is they further took postmenopausal women as they being more susceptible to urinary tract infection. One of the, and most effective recommendation that we came out with this dissertation is giving vitamin D therapy (through supplementation and exposure to sunlight), with antimicrobial therapy for such infections, so that faster recovery and less incidence of the recurrent infection.

5. Conclusion

Our research on women of reproductive age with low vitamin D levels reveals that they are more at risk of contracting UTI than the healthy ones. This show a significant association of vitamin D deficiency and urinary tract infections especially in moderate and severe infections, which is an important aspect of infection control. Furthermore, with the increasing development of antimicrobial resistance in gram-positive and -negative bacteria being a worldwide concern, vitamin D supplement could be used in combination with antimicrobials to improve the management and therapy of UTI, especially in cases of multi-drug-resistant infections. Concluding that to treat women, at reproductive age, with the urinary tract infections (whether acute or recurrent), it is better to search for vitamin D deficiency and treat it simultaneously. This will be more convenient for both the health care system and patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

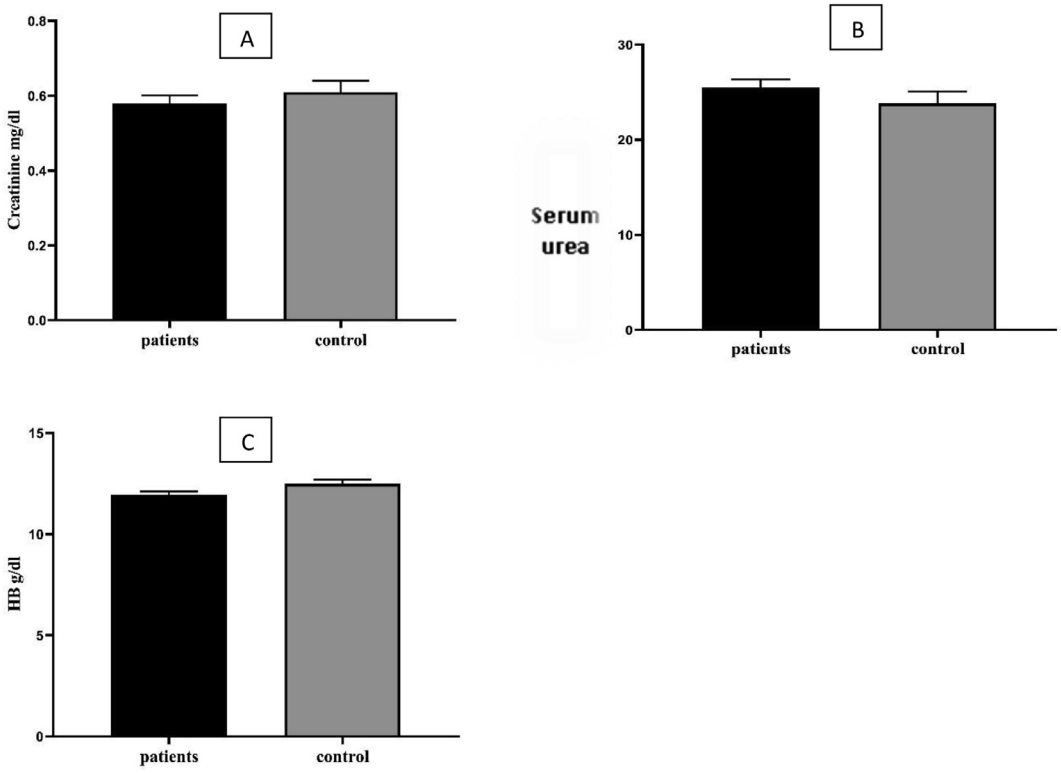

Fig. 4. Analysis showed that the serum creatinine (A) and urea (B) and blood hemoglobin (C), are normal in the (case) patients group studied which is similar to the control groups.

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