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Estimation the level of zonulin, antioxidant factors and some biochemical parameters in renal failure patients

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***Abstract*---**The kidneys are important organs similar in shape to beans located on both sides of the spine and their function is to filter water and toxic substances from the blood. The kidneys, like other members of the human body, are exposed to failure due to many factors that ultimately lead to kidney damage. About five millimeters of one hundred samples from dialysis patients were kept in test tubes designated for this purpose, where the samples were stored at appropriate temperature until the required number was completed, the same measures were also taken on the healthy group, which numbered fifty samples, and their ages were approximately equal to the ages of the dialysis patients. As for the results of the current research, it was proved that there was a significant increase in the levels of zonulin and the capacity of total antioxidants, urea, creatinine and glucose in dialysis patients compared to the control group. As for glutathione, there is no significant change. In addition, scientists have proven that one of the most important causes of kidney failure is the high level of glucose in the blood, and due to the lack of functional efficiency of the kidneys, the level of urea and creatinine increased, and all these evidences are identical with the results of the current research. Scientists have proven in many research that the results of the current research are compatible with those research, where the researchers attributed that the reason for the high level of zonulin is due to the inflammatory immune response caused by nephritis, which leads to an increase in free radicals due to the inefficiency of the kidneys and for the same reason leads to a decrease in the level of glutathione.

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Introduction

The kidneys are two reddish-brown colored bean-shaped organs in vertebrates. It is situated on the left and right, and the length of a grown-up human is around 12 cm (4 + in) [1]. The kidneys are divided into two main parts: the cortex and the medulla. The interstitial arteries then, at that point, supply blood to the curving courses that pass through the limit of the cortex and the marrow [2]. The kidneys are related to controlling the volume of various body fluids, fluid osmolality, corrosive base equilibrium, different electrolyte centers, and detoxification. Filtration occurs in the glomerulus: a fifth of the volume of blood that enters the kidneys is filtered. Examples of reabsorbed substances are free water, sodium, bicarbonate, glucose, and amino acids [3]. kidneys play a significant role in regulating the internal environment's integrity. First, the blood that passes through the kidneys is filtered (glomerular filtration) such that all components, except blood cells and plasma proteins, join the micro tubular network. The useful Innocuous substances are reabsorbed rapidly in the kidneys, but undesirable substances avoid filtration and are deliberately excreted in urine [4]. The trend in modern medicine for kidney diseases has increased due to the consideration of kidney disease as one of the most important factors that cause some other complex diseases, these include genetic susceptibility, immune disorders, diabetes, and high blood pressure. Specialists suffer from the difficulty of diagnosing kidney diseases due to the multiplicity of pathogens that overlap with the causes of kidney diseases [5].

Zonulin

Zonulin is a haptoglobin protein that modulates the permeability of the tight junctions between intestinal cells [6]. Zonulin increases the permeability of the epithelium layer of the small intestine. It is the fair physiological mediator that raises gut permeability by modulating the intercellular tight junction (TJ), while the appropriate role of the TJ is to maintain normal physiological processes in the intestine. Systemic inflammation can lead to zonulin expression or local inflammation [7]. The level of Zonulin is an indicator of diabetes patients as when the level of Zonulin increases, it leads to complications of diabetes for patients. The field of study relates to diabetics and prevents them from accessing complications that damage the eye, kidneys, and diabetic feet [8].

Total antioxidant capacity

Total antioxidant capacity is defined as an important biochemical parameter for assessing the overall antioxidant status of plasma and body fluids formed from ingestion or production of antioxidants, and their consumption in normal or increased amounts of ROS production [9]. Wherein the capacity of known and unknown antioxidants and their synergistic interactions are evaluated, thus an insight into the delicate balance between oxidants and antioxidants is given in the organism [10]. Oxidative stress plays a significant part in sickness progression

and the development of cardiovascular complications in patients with chronic kidney disease (CKD). A few examinations have recommended changes in the peculiarity of oxidative pressure, through the development of responsive oxygen species on the outer layer of hemodialysis membranes and polymorphous leukocyte activation in patients undergoing hemodialysis (HD) [11].

Glutathione (GSH)

Glutathione is known as one of the antioxidants in flowers, animals, fungi, and some micro and archaic organisms, a tripeptide with a gamma peptide linkage between the carboxyl gathering of the glutamate and cysteine face chain. The carboxyl-regulation of cysteine residues is connected through the limiting of the ordinary peptide to glycine [12].

Creatinine

Creatinine is known as nitrogenous organic acid (Cr, -N-methylguanidino acetic acid). derived from the non-enzymatic breakdown of creatine (amino acids) in muscle. The production and excretion of creatinine by the kidneys determines the level of creatinine in the blood (SCr). Creatinine is dispersed through total body water, and is eliminated out of the blood by the nephron after that excretion out with urine without reabsorption by tubules cells [13]. The level of creatinine in plasma is directly related to muscle mass and indirectly related to GFR, so any failure in GFR will lead to an increase in plasma creatinine level [14].

Urea

Urea is a product of protein metabolism formed in the liver cells from ammonia gas that results from the deamination of amino acids [15]. Urea plays an important role in the metabolism (especially catabolism) of nitrogen-containing compounds. It is one of the most important metabolic nitrogen compounds that is excreted through urine [16]. The urea is filtered in the glomerulus, and about 50% of filtrated urea is reabsorbed in the renal tubules. Therefore, blood urea level cannot be considered as the main standard in the calculation of kidney function, whereas creatinine, which is totally excreted without reabsorption, can calculate the kidney function [17]. The concentration of urea increases when production is increased with high protein intake, tissue damage, trauma, hemorrhage, or glucocorticoids. On the other hand, urea decreases when production is decreased with low protein intake and liver failure [18].

Subjects & Methods

The current study included a hundred individuals on dialysis who were suffering from renal failure. Their ages ranged from 16 to 70 years old. These patients were enrolled in Al-Sader Medical City in the governorate of AL-najaf AL-ashraf. After receiving permission from hospital management, a blood sample was collected from them. The control group consisted of sixty healthy people. Their age range is comparable to that of the patients. A total of five milliliters of venous blood samples were drowned.

The blood was separated into two parts: the primary, about 1.5 mL, was placed in an EDTA tube and measurements were taken immediately; the rest, about 3.5 mL, was placed in a serum tube, After being allowed at room temperature for 10 minutes to clot, centrifuged at 3000 Xg for 10 minutes to separate the serum, and lastly transferred into fresh disposable tubes and frozen at (-70 C) until analyzed, the serum was spun at 3000 Xg for 10 minutes to separate the serum. [19]

The benchmarks that were focused on in the current research were made through the ELISA technique, namely, zonislin, glutathione and TAC, while glucose, creatinine and urea were measured by spectrophotometry. [20] Statistical analysis: The data collated after biochemical analysis were subjected to statistical calculation using statistical software (Megastat). The mean, standard deviation of mean, F-distribution test were obtained. Critical value or test of probability less than 0.05 ($p< 0.05$) was regarded significant also we use Microsoft Excel (2010), SPSS17 and Minitab v. 14 .[21]

Result and Discussion

Characteristics

In this study, some of the demographical characteristics were assessed by analyzing questioners answered by direct interviews with control and case groups as indicated see table (3-1).

Table (3-1): The demographic characteristics the of study

The characteristics		Patients	Control	
Total (No.)		100	60	
Age (mean ± SD)		47 ± 14.58	47 ± 14.84	
Sex	male	46	29	
	female	54	31	

Table (3-2) result of parameters for patients with CKD undergoing dialysis and their control

Parameter	Patients		Control		P value
GSH	5.55±1.4		5.42	0.66	0.55561
Zonulin	315.74	120.54	267.72	91.97	0.03938
Total antioxidants	3.98	5.057	2.59	0.94	0.043105
S Cr	8.87	3.22	4.17	4.3	3.44E-06
B.U	165.66	58.03	94.05	69.35	1.18E-05
GLU	166.29	127.46	112.57	29.19	0.002731

Zonulin

Table (3-2) shows a significant increase (p value = 0.03938) in level of zonulin in renal failure patients (315.74) as compare with the control group (267.72).

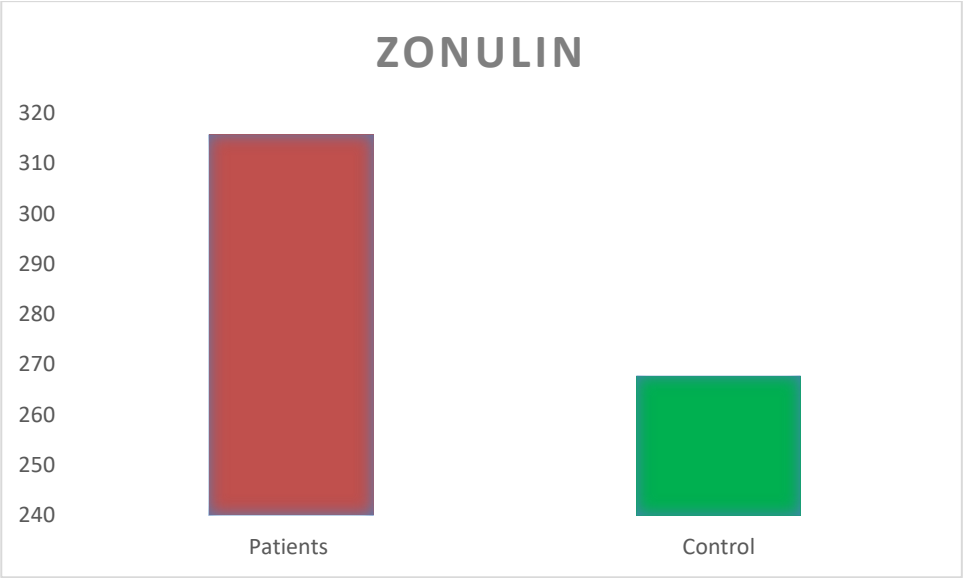


Figure (3-1) shows level of zonulin in patients and control in renal failure

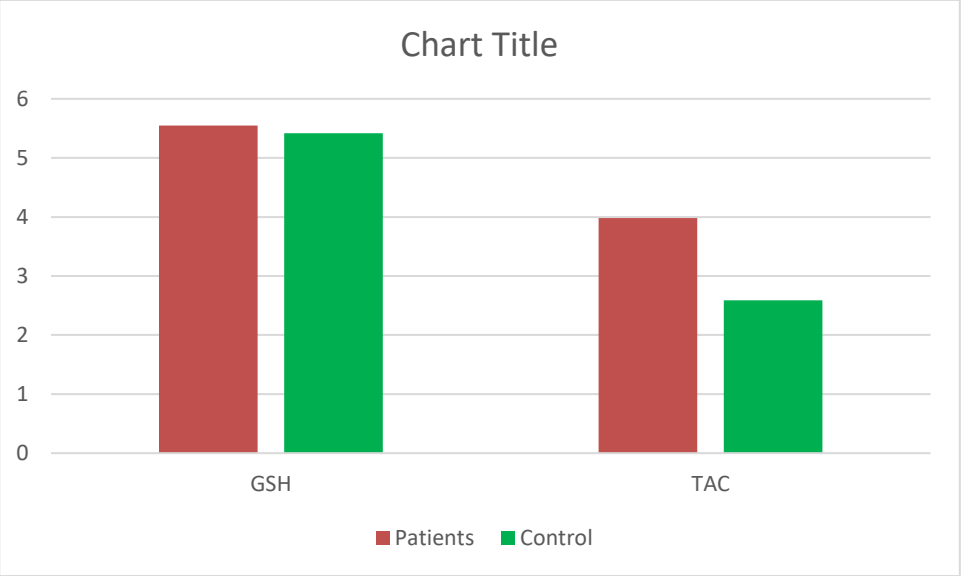
Zonulin is the only physiological reversible protein regulation of tight junctions in the human body. The zonulin regulates the narrow junctions through ... as well as the secretion of a liquid substance on the lumen of the intestine whose function is to prevent bacterial colonization [22] In a new study, it was proven that zonulin levels in kidney patients are higher than the control group, the researchers attributed the increase in zonulin plasma to kidney patients due to the accompanying renal failure of some infections that would increase the level of zonulin[23]. Another study in which the relationship between intestinal permeability and inflammation was studied in hemodialysis patients, where scientists found that increased intestinal permeability increases the severity of chronic inflammation, which in turn increases the level of zonulin as an immune response.[24] It is the most important research that is in line with the current research conducted by the scientist (Lukaszyk ,*et al*; 2018) in which it was proven that zonulin has a high significant relationship with anemia and inflammation.[25] In another study challenging the results of the current research, where it was proven in this research that zonulin has no significant relationship to iron cases, as well as the indication of the results of this research that the level of zonulin is low in patients with renal failure compared to healthy people, the reason for the difference in the results is that patients are taking treatments that weaken Immunity and thus leads to a decrease in the level of zonulin in patients.[26]

In another study, which was agreed with the current results, where it was proven in this study that there is a significant relationship between zonulin and the systemic inflammatory response, the results of this research gave accurate

support to the results of the current research, as the results showed a noticeable increase in zonulin levels in patients compared to the control group.[27]In addition, there is another research in which the researchers prove that there is a significant increase in the levels of zonulin in patients with kidney disease with diabetes when compared to the control group without diabetes this confirms the existence of a close relationship between high zonulin and high blood sugar compared to the control group, so the results of the current research gave a great similarity with that research.[28]

Antioxidant

In the same table (2-3) the oxidation factors (GSH & TAC) indicate a significant increase (p value = 0.043) in Total Antioxidants Capacity (3.98) Compared to the control group (2.59), no significant change (p value = 0.55) in glutathione level in patients with renal failure (5.55) When compared with the control results (5.42).



In another research developed for the purpose of studying the relationship between zonulin and antioxidants, the scientists found that the level of total antioxidant and zonulin rise significantly in patients with renal failure when compared to the group.[29] In a study conducted to investigate the relationship between glutathione and the total antioxidant capacity in kidney patients, the researchers proved a significant decrease in the level of glutathione, while they found on the contrary with regard to the level of total antioxidant capacity, a significant increase in its level in kidney patients as compared to the control group. [30] To show the difference between the previous research and the current research in the results related to the level of glutathione, it is attributed to the treatment that kidney patients take, as they take some treatments that improve the level of glutathione for the purpose of overcoming the oxidation products harmful to human life and thus reducing the side effects resulting from the lack of glutathione level in the blood.[31] [32] Research indicates in its study of the causes of the deficiency of glutathione level in patients with dialysis that the

reason is due to the increase in oxidative factors in patients due to the inefficient work of the kidneys, which leads to the consumption of higher levels of antioxidants, and this is proven by the results of the current research.[33] The results of the current research were also supported by the research in which the scientist (Ozer *et al*; 2003) proved that the lack of efficiency of the kidney and its failure to work in an acceptable manner led to an increase in oxidation products due to the low levels of antioxidants, including glutathione.[34] In a research published in the Wiley Journals group, which included a large number of patients with kidney failure and kidney stones, the research dealt with a study to show the level of total antioxidant capacity for a large number of patients, which reached)9777(people. The researchers found that the level of total antioxidant capacity increases significantly in Dialysis patients (kidney failure), but there is a non-significant increase for patients with kidney stones, and this is fully consistent with the results of the current research.[34] In addition, in the same research referred to above, the researchers compared the levels of total antioxidant capacity between men and women and found that the levels of total antioxidant capacity in men are higher than their levels in women, which confirmed the conclusion that proves that men are more susceptible to kidney failure than women. all of these conclusions are consistent with the results of the current research.[35] Total antioxidant capacity (TAC) is the measure of the amount of free radicals scavenged.[36] In a research devoted to the reason for the high level of total antioxidant capacity before dialysis and the reasons for its low levels after dialysis, the scientists found that the reason for the high level of total antioxidant capacity is due to the high levels of free radicals, which leads to the immune weakening of the body, so that body perform defensive functions for the purpose of cleaning more Possible amount of free radicals leads to an increase in the levels of total antioxidant capacity and this is consistent with the current research and explains why this clinical parameter is high. Kidneys and detoxification, which leads to a decrease in the level of total antioxidant capacity in the blood.[37] The correlation between zonulin and (GSH, TAC) in patients with renal failure

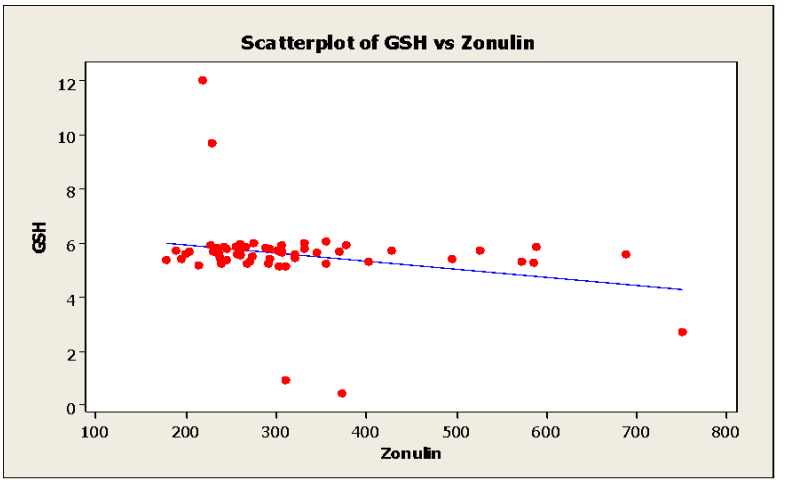
Table (3-3) refers to the correlation between zonulin and (GSH, TAC) in patients with renal failure

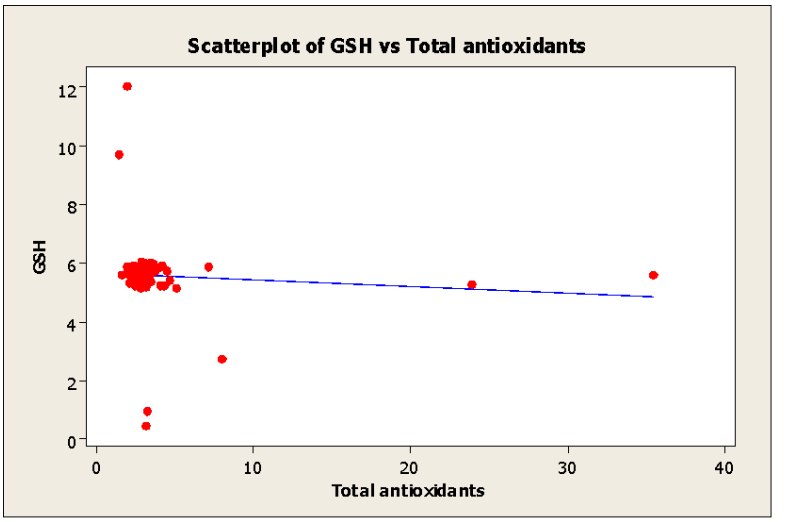
r/P Value	GSH	Zonulin
Zolulin	-0.257/ 0.047	
Total Antioxidant Capacity	-0.081/ 537	0.603/ 0.001

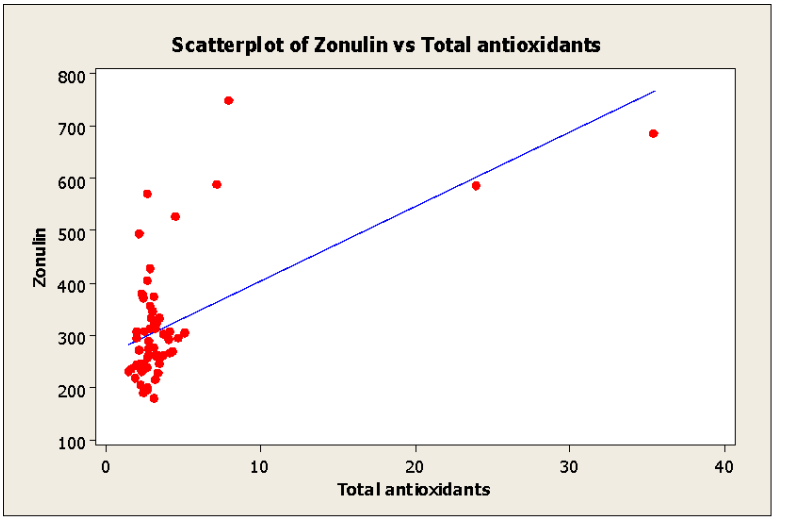
The table (3-3) shows a significant slightly negative correlation (r = -0.257 & P Value = 0.047) between zonulin and GSH, in the same table appeared no significant correlation between GSH & TAC (r = -0.081 & P Value = 0.537) while a significant positive relation between Zonulin & TAC (r = 0.603 & P Value = 0.001) in patients with CKD

Concerning the research related to the study and the vital values and values of hemodialysis patients, most of the research agrees on the existence of a positive significant relationship between zonulin and TAC, as both items rise according to a mechanism specific to each of them, where the level of zonulin rises as an immune response as a result of the occurrence of inflammation in dialysis patients, while TAC It rises as a result of the high level of free radicals due to the

lack of efficiency in the work of the kidneys. This mechanism makes both items rise under the same conditions, which gives the possibility of a direct relationship between them.[38] ,[39] . in addition Other research proves the inverse significant relationship between glutathione and zonulin, where glutathione expresses the level of antioxidants in dialysis patients compared to the level of the immune response of the same patients by zonulin, where most research confirms that inverse relationship that is consistent with the results of our current research.[40] Perhaps one of the most important contradictions that exist in the current research, which does not agree with the research that preceded that research, where the results of the current research showed that there is no significant relationship between glutathione and TAC, and the reason is that patients take glutathione as a treatment for the purpose of reducing the severity of the side effects that may result from a low level Glutathione, which leads to a relative increase in glutathione levels, and an imbalance occurs in the relationship between glutathione and TAC[31].







Creatinine, urea and glucose

The results of the research indicate a significant increase in its levels in dialysis patients compared to the control group. Many studies confirm and agree with the current research, where scientists have proven that dialysis patients suffer from a significant increase in the levels of creatinine, urea and glucose. The scientists attributed this rise due to several factors, the most important of which is high pressure, which in turn leads to stress on the kidneys and its lack of functional efficiency and thus damage to the nephrons, in addition, the high level of sugar leads to great damage and damage to the kidney, and this is confirmed by the results of the current research [41].

Conclusions

Through the findings of the results, we conclude from that there is a significant increase in the level of zonulin and TAC in dialysis patients when comparing their results with the control group, and the reason for this is due to the immune response, which in turn increases the levels of zonulin, while the increase in TAC is due to the increase in the amount of free radicals in Patients due to the insufficiency of the kidneys. As for glutathione, there is no significant difference in patients compared to the healthy group. The reason is attributed to the patients taking some treatments that would compensate for the decrease that occurs in glutathione levels.

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