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Research Article
Effects of Smoking and Body Mass Index on Serum Liver Enzyme Levels in Chronic Kidney Disease Patients on Hemodialysis

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Abstract

Background and Objective: A markedly elevated liver enzyme levels (GGT, AST and ALT) are commonly associated with liver disease but recently has also been linked to an increased risk of chronic kidney disease (CKD). Therefore, this study was carried out to measure the serum levels of GGT, AST and ALT in Iraqi adult patients with CKD. **Materials and Methods:** The levels of GGT, AST and ALT were measured in 30 controls and 30 CKD patients before the hemodialysis session. The effects of age, gender, smoking status and body mass index (BMI) on the levels of liver enzymes were investigated. **Results:** Compared with the controls, CKD patients had a significantly higher level of GGT ($p<0.05$), whereas, no significant associations between the levels of ALT or AST and risk of CKD were observed. There were no significant differences between male and female with regard to GGT, ALT and AST levels in patients or the controls. The GGT levels were significantly reduced with age in patients and the controls ($p<0.05$). The GGT levels were significantly higher in smokers than in non-smokers for patients and the controls. For patients and the controls, the GGT levels were significantly higher in overweight and obesity subjects than in normal BMI subjects ($p<0.05$). By contrast, the age, cigarette smoking and BMI did not significantly affect the ALT and AST levels in patients or the controls. **Conclusion:** The GGT level was elevated in CKD patients on hemodialysis without the elevation of other liver enzymes in the middle-aged and elderly in Iraq. Smoking and BMI were positively associated with elevated levels of GGT in CKD patients. Therefore, these findings suggested that maintaining a healthy weight and smoking cessation might reduce the GGT level and may also prevent or delay the onset of CKD and improve health overall.

Key words: Body mass index, chronic kidney disease, gamma-glutamyltransferase, hemodialysis, cigarette smoking

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Chronic kidney disease (CKD) is abnormal kidney function and/or structure. CKD recently appears to be a quite common and often goes unrecognized[1]. The chance of developing CKD is present at all ages and regardless of sex and race. The risk of CKD increases dramatically with age and is more common in females than males[2]. It has been estimated that about 8 to 10% of the adult population had experienced some form of kidney health problems. Moreover, millions of people are dying prematurely every year as a result of CKD complications. Statistical data about the prevalence of CKD is quite limited in many countries in the Arab world, including Jordan and Iraq[2,3]. However, some previous reports indicated that the prevalence of CKD is high in some Arab countries, including Saudi Arabia and Egypt[2,4].

CKD often exists together or associated with other conditions including cardiovascular disease, diabetes hypertension and obesity[5]. Therefore, a high prevalence of diabetes, hypertension and coronary artery disease among the Arab population might explain the high incidence of CKD. Moreover, proteinuria, smoking, chronic use of non-steroidal anti-inflammatory drugs and hypercalcemia are also all risk factors for the progression of CKD[5-7].

Generally speaking, the treatment options for CKD and care planning have recently been improved. These options include lifestyle changes, medication, hemodialysis (HD) and kidney transplant[1-3]. Despite all the recent advances in the diagnosis and treatments of CKD, this disease still remains a major cause of morbidity and mortality in the world. It was also noticed that some patients went without treatment, and/or they were turning for treatment in the black market, especially in developing countries, such as Jordan and Iraq. This was due to the rapid increase in the treatment costs for CKD during the last decade. It has been estimated that the cost of treating all CKD cases ranges from $12 billion in Australia to 48 billion in the USA. In both developing and developed countries, the cost of treating patients with advanced CKD is extremely high and constitutes a significant proportion of their health care expenses[4-8]. Therefore, an earlier diagnosis and treatment of the underlying cause of CKD will help in early intervention, slow further progression or damage to the kidney, prevent CKD or might avoid early deaths as well as reduce the need for the high cost of treatment and long-term HD and kidney transplantation.

It has been well documented that the serum levels of gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT) and aspartate amino transferase (AST) are widely used as the biomarkers of liver function and to monitor hepatic diseases as well as to assess the overall health status of individuals[9,10]. There is a growing body of evidence indicating that high blood levels of GGT, ALT and AST are associated with increased risk of diseases and all-cause mortality[5-11]. Therefore, the reported association between the elevated serum GGT, ALT and AST levels and other diseases appear to be complex. Moreover, the mechanisms underlying this association also need further investigation.

The serum levels of GGT, ALT and AST may differ depending on the age, sex and the status or the health condition of individuals and may vary over time[11]. Several investigations reported that the serum levels of GGT, ALT and AST decreased near the lower end of the range of the normal values in CKD patients undergoing peritoneal dialysis and HD for reasons that remain unclear[5-7]. Similarly, the serum of GGT level was found to be negatively associated with a function in patients with CKD[12]. Recently, Abo Bker *et al.*[8] showed that the serum AST and ALT levels were significantly declined in kidney dialysis patients. Contrary to the findings of these studies, a recent study reported that GGT level was high in end-stage kidney dialysis patients and was an independent risk marker for all causes and cardiovascular death[13].

Overall, the potential association of these enzymes and the exact cause of fluctuations in CKD patients remain controversial topics. These topics are still highly debated among biomedical researchers and have led to more questions than answers. In addition, no studies have been carried in Iraq and little is known about the levels of these three enzymes in patients with CKD in this area. Therefore, the current study aimed to examine the association between CKD and serum GGT, ALT and AST levels in CKD patients on HD and in the apparently healthy individuals in the Iraqi people. In addition, the effects of age, gender, body mass index (BMI) and cigarette smoking on the serum GGT, ALT and AST levels in these patients were investigated.

MATERIALS AND METHODS

Study population: A total of 30 patients with CKD on HD were included in this study. In addition, thirty healthy control subjects of Iraqi citizens who were closely matched for age and gender were also included for comparison. The study was conducted at Alyarmouk Hospital during March-May 2017. This hospital is located in Baghdad city, in the District of Al Qadisiyah, Iraq.

In this study, CKD was defined by serum creatinine of 150 mmol L^{-1} (1.7 mg dL^{-1}) and a GFR of less than 60 mL $min^{-1}/1.73\ m^2$. Also, this disease was referred to chronic, if the symptoms last at least 3 months and only patients undergoing HD were allowed to participate in this study.

For this study, a protocol with ethics approval was required. The ethical approval was obtained by a research ethics committee of Alyarmouk Hospital in Baghdad city. In addition, informed consent was given to each participant and a signed consent form was obtained from all participants. The inclusion criteria consisted of an age of 18 years or older, had CKD and undergoing HD for a minimum of at least three months, the ability to communicate with interviewers and they volunteered to participate in the study. The recruited participants regularly visited the dialysis unit in the hospital. Both patients and the controls were also excluded for the following conditions: Alcoholic or had been previously diagnosed with heart and liver diseases such as acute myocardial infarction, pulmonary emulsion, acute pancreatitis, viral and toxic hepatitis and acute cirrhosis as well as cancer diseases, hypertension and diabetes.

Data collection: Information about patients and the controls was collected using a structured questionnaire. A lifestyle questionnaire was designed to obtain all personal and health information. The data included the volunteer's address and contact number, age, height and weight and if they smoke cigarettes. The collected data also included the personal and the family medical history of any kind of kidney problems, the duration of the CKD and the name of medication or drugs taken during the treatment.

To assess the effects of BMI as a health-related factor on the serum levels of GGT, ALT and AST, the height and weight were measured for all participants. Then, BMI value for each participant was derived from the calculation of weight in kilograms divided by the square of the height of an individual in meters (kg m^{-2}). After that, the controls and patients were divided into four subgroups according to the World Health Organization (WHO) definition of BMI (WHO)[14]. BMI ranges were divided as follow:

- 18.5< kg m^{-2} : Underweight
- 18.5-24.9 kg m^{-2} : Normal weight
- 25-29.9 kg m^{-2} : Overweight
- >30 kg m^{-2} : Obese

Collection of blood samples: Under aseptic precautions, 5 mL blood sample was carefully drawn from each participant from the vein in the antecubital fossa prior to the dialysis session using sterilized disposable syringes. The blood sample was placed immediately into 10 mL EDTA vacuum tubes. The blood sample was allowed to clot at room temperature for 30 min. For serum collection, the blood sample was then centrifuged at 1500 rpm for 5 min. Then, the serum was placed in a new 5 mL micro centrifuge tube. After that, each tube was marked with a sticker and given an identification code and stored in ice. Finally, the GGT, ALT and AST levels in each serum sample were measured as described below.

GGT assay: A colorimetric assay method was used for determination of the GGT level in the serum samples. A GGT-Kit was purchased from the Gen-Way Biotech company (Gen-Way Biotech Inc., Nancy Ridge Dr, San Diego, CA 92121 USA). The GGT assay procedure was carried out according to the manufacturer's instruction provided by the company. Each serum sample was done in triplicate and the mean value of triplicate measurements was calculated.

AST assay: To measure the AST level, a colorimetric enzymatic assay for the determination of the AST in serum samples was conducted according to the manufacturer's instruction (Xpress Bio, Life Science Products, P.O. Box 458, Thurmont, MD 21788, USA). Each serum sample was run in triplicate and the mean value of triplicate measurements was calculated.

ALT assay: The level of ALT in each serum sample was measured using a direct enzymatic colorimetric assay. A AST kit was purchased from Spectrum diagnostics company (MDSS GmbH, Schiffgraben 41, 30175 Hannover, Germany).The ALT assay was performed according to the procedure described by the manufacturer's instruction. Triplicate measurements of each sample were performed and the mean value for each sample was calculated.

Statistical analysis: All the data were expressed as the means±standard deviation (SD) or percent (%). Normality was checked before any analysis. The differences between groups were analyzed by independent t-test using SPSS software (version 16.0) as appropriate. A P-value of $\leq$0.05 was considered to be statistically significant.

RESULTS

This study was carried out to measure the serum GGT, AST and ALT levels in patients with CKD on HD. To accomplish this investigation and search for any association between these three serum liver enzymes and CKD, 30 patients with CKD and 30 healthy control subjects matched by age and gender were recruited during the study period as shown in Table 1. The majority of studied patients and the controls were males (63% male patients and 67% male controls). In addition, there were 20 (66.7%) patients with CKD aged 40 years or older.

Table 1: Summary of characteristics of the study participants

Parameters	CKD patient N (%)	Control N (%)
Gender		
Male	19 (63)	20 (66.7)
Female	11 (37)	10 (33.3)
BMI		
18.5-24.9 (kg m^{-2})	8 (27)	10 (33)
25-29.9 (kg m^{-2})	15 (50)	14 (47)
> 30 (kg m^{-2})	7 (23)	6 (20)
Age		
<40 years	10(33.3)	10 (33.3)
≥40 years	20 (66.7)	20 (66.7)
Smoking		
Yes	11 (37)	10 (33.3)
No	19 (63)	20 (66.7)

All values are the number and percentage in parentheses. CKD: Chronic kidney disease, N: Number of subjects

Similarly, 20 (66.7%) subjects were 40 years or older in the control group. The age distribution of patient group (a range of 17-72 years) was closely similar to the control group (a range of 24-75 years).

Among patients, 50% (11 males and 4 females) were overweight and 23% (5 males and 2 females) were obese as shown in Table 1. For the control group, 47% (9 males and 5 females) were overweight and 20% (3 males and 3 females) were obese. Based on smoking status, all participants were classified into two groups: Smokers and non-smoker. Among patients, 37% (8 males and 3 females) were regular smokers. Similarly, 33% of the controls were male regular smokers. None of the participants had a history of the following diseases: Liver diseases, heart diseases, cancer, hypertension or diabetes. All participants denied alcohol consumption.

The GGT level in the control group was 17±14 U L^{-1}, whereas GGT level in patients was 56±21 U L^{-1} as shown in Fig. 1. Statistically, patients had a significantly higher GGT level than the controls ($p<0.01$). On the other hand, the ALT levels in the control group and patients were 19±13 U L^{-1} and 18±12, respectively. Similarly, the AST levels were 19±12 in the control and 19±14 in patients. Statistical data analysis revealed no significant associations between the level of ALT and risk of CKD as well as between the level of AST and risk of CKD.

The data in Table 2 revealed that the level of GGT for males with CKD was slightly higher than that for females with CKD, although the difference did not reach a statistical significance. Similarly, the gender of patients did not significantly affect the ALT and AST levels in patients or the controls. A significant elevation of the GGT level was seen in CKD patients compared to the controls regardless of gender.

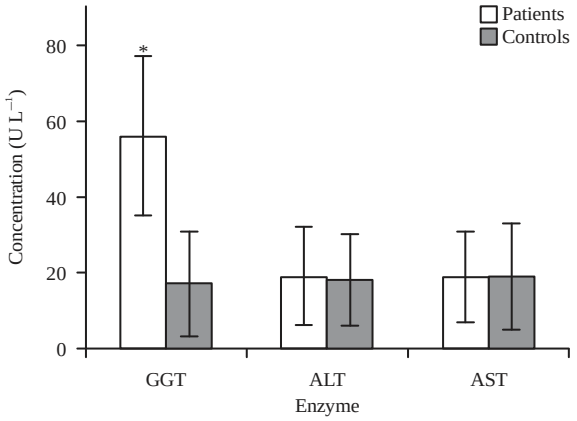

Fig. 1: Mean values and standard deviations of the serum gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in patients with chronic kidney disease. U L^{-1} is units per liter. An asterisk indicates a statistically significant difference in the mean GGT levels between patients and controls ($p<0.05$)

By age, it can be seen in Table 2 that the GGT levels changed significantly from the average of 73 U L^{-1} in patients less than 40 years old to 43 U L^{-1} in patients aged ≥40 years ($p<0.01$). Also, the level of GGT in the serum was found to be decreased significantly with age from 26 U L^{-1} in the control subjects of less than 40 years old to 9 U L^{-1} in the control subgroup aged 40 years old and above ($p<0.05$). In subgroups based on age in this case-control study, patients had a significantly higher level of GGT as compared with the controls. In contrast, no significant differences in the ALT and AST levels were found between and within the two subgroups of the controls and patients ($p> 0.05$). Moreover, the data indicated that there was a tendency for a decrease in the serum mean levels of GGT, ALT and AST in both the control and patient groups with increasing age.

It was obvious that the smoker patients had a significantly higher GGT level than the non-smoker patients as shown in Fig. 2 ($p<0.01$). The GGT level in the smoker control was significantly different from those observed in the non-smoker control ($p<0.01$). By contrast, no significant differences in the ALT or AST levels were noted in the smoker patients as compared to the non-smoker patients. A similar finding was also observed in the ALT and AST levels between the smoker controls when compared to the non-smoker controls.

To investigate the association between the serum levels of GGT, ALT and AST and CKD status, without the confounding influences of overweight and obesity, the study subjects were

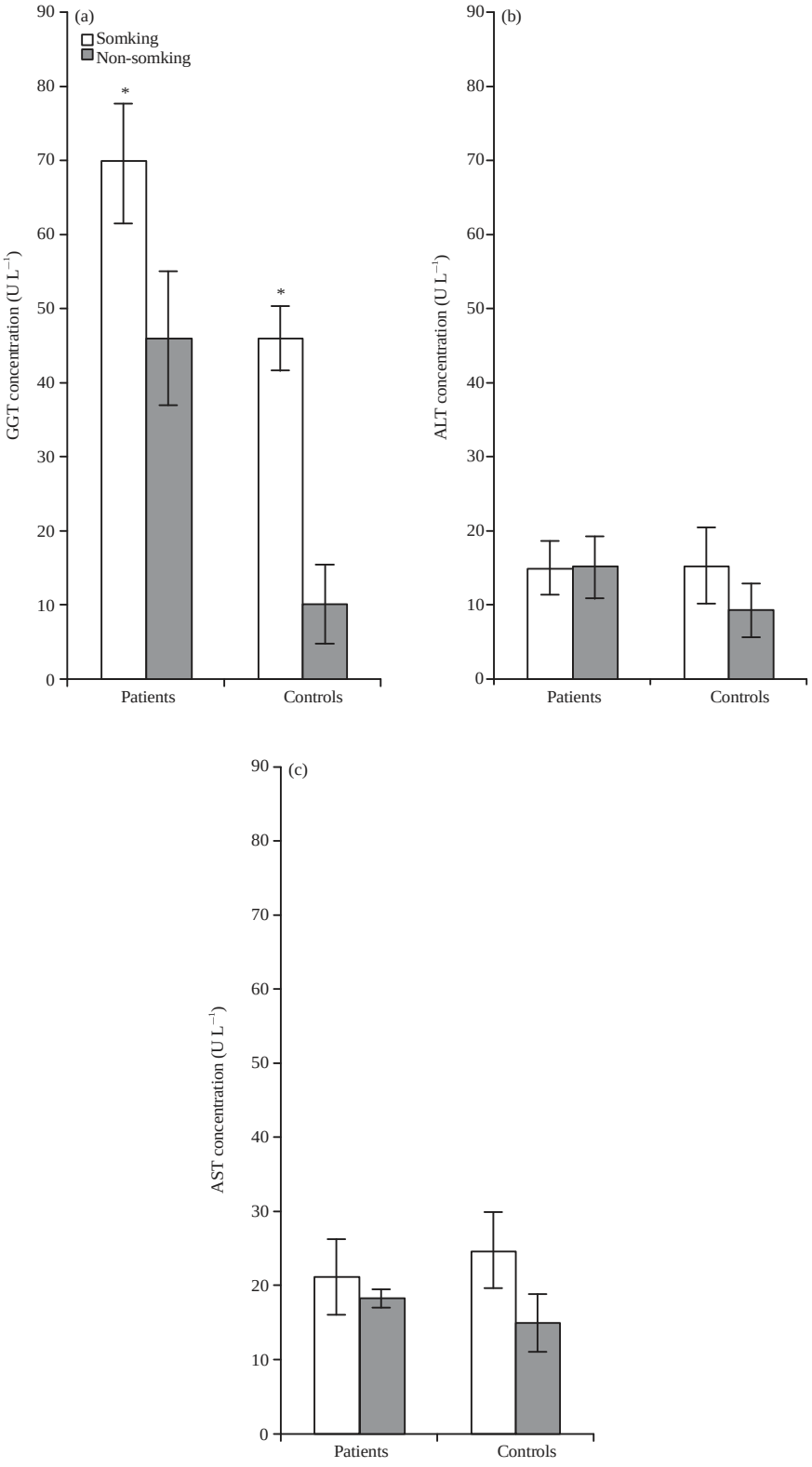

Fig. 2(a-c): Effects of cigarette smoking on the serum levels of (a) Gamma-glutamyl transferase (GGT), (b) Alanine aminotransferase (ALT) and (c) Aspartate aminotransferase (AST) in patients with chronic kidney disease. U L^{-1}: Units per liter. Values are means±standard deviations. An asterisk indicates a statistically significant difference in the mean GGT levels between smoker and non-smoker individuals ($p<0.05$)

Table 2: Effects of gender and age on the serum levels of gamma-glutamyl transferase (GGT), alanine amino transferase (ALT) and aspartate amino transferase (AST) in patients with chronic kidney disease

	GGT				ALT				AST			
	Patients		Controls		Patients		Controls		Patients		Controls	
Parameters	U L^{-1}	N	U L^{-1}	N	U L^{-1}	N	U L^{-1}	N	U L^{-1}	N	U L^{-1}	N
Gender												
Male	41±30[a]	11	20±12[b]	11	12±8	11	14±13	11	16±12	11	24±15	11
	28±22[a]	19	15±8[b]	19	19±18	19	9±6	19	22±13	19	18±7	19
Age (years)												
<40	73±16[a]	11	26±16[b]	11	43±18[b]	19	9±3[a]	19	16±13	11	14±11	11
≥40	13±13	19	9±7	19	23±14	11	21±15	11	16±16	19	17±5	19

Data are represented as means±standard deviations. U L^{-1}: Units per liter. N: Number of subjects. Different letters (a and b) within columns indicate a statistically significant difference ($p<0.05$). Same letter (a and b) between two columns indicate a statistically significant

Table 3: Effects of BMI on the serum on serum levels of gamma-glutamyl transferase (GGT), alanine amino transferase (ALT) and aspartate amino transferase (AST) in patients with chronic kidney disease

	GGT				ALT				AST			
	Patients		Controls		Patients		Controls		Patients		Controls	
BMI (kg m^{-2})	U L^{-1}	N	U L^{-1}	N	U L^{-1}	N	U L^{-1}	N	U L^{-1}	N	U L^{-1}	N
18.5-24.9	17±12[a]	8	8±6[a]	10	13±15	8	14±13	10	13±11	8	15±12	10
25-29.9	47±19[b]	15	23±11[b]	14	15±14	15	16±10	14	17±13	15	23±17	14
>30	80±14[c]	7	38±12[c]	6	19±12	7	18±16	6	18±14	7	26±24	6

Data are represented as Means±Standard deviations. U L^{-1}: Units per liter, N: Number of subjects, BMI: Body mass index, Different letters (a, b and c) within columns indicate a statistically significant difference ($p<0.05$). Same letter (a, b and c) between two columns indicate a statistically significant

stratified in three categories of normal, overweight and obese using WHO definition of BMI as shown in Table 3. Based on the calculated BMI, the GGT levels were significantly higher in high BMI than that in CKD patients with low BMI ($p<0.05$). Similarly, the GGT levels were significantly higher in the overweight/obese controls than that in the normal BMI controls ($p<0.05$). More importantly, patient categories had significantly higher GGT levels than the control categories regardless of BMI ($p<0.05$). On the other hands, among the three BMI categories of patients and the controls, the ALT and AST levels were slightly higher in overweight/obese subjects compared with the normal weight subjects. The results indicated that there were no statistically significant differences in ALT or AST levels between patient and the control categories with regard to BMI.

DISCUSSION

To our current knowledge, this is the first case-control study to explore the association of the serum GGT, ALT and AST levels with CKD in Iraqi people. The current investigation revealed that the mean values of serum GGT, ALT and AST levels for the control group (non-CKD individuals) were 19.1, 11.3 and 18.13 U L^{-1}, respectively. It is a fact that the reference values of the serum GGT, ALT and AST levels for adults may slightly vary between laboratories. For some laboratories, the reference ranges of the serum GGT, ALT and AST for adults were reported to be closely similar and range from 0-45 U L^{-1} [15]. Other labs reported that the normal ranges of the serum GGT, ALT and AST levels were between 0-45 U L^{-1}, 7-56 and 10-40 U L^{-1}, respectively[16,17]. Based on the reference ranges, the measured levels of the serum GGT, ALT and AST of our control group were in accordance with the reference ranges that were published previously.

Most importantly, data analysis revealed that only the serum GGT level significantly increased in patients on HD when compared to the apparently healthy individuals in Iraqi people. While the serum levels of ALT and AST were similar for CKD patients and the controls. In addition, the mean GGT level was at least two times greater than the upper reference value in nearly most of the patients with CKD. On the other hands, the ALT and AST levels for CKD patients and the control participants were near the lower limits of the normal reference ranges for most labs. Therefore, this current study suggested that the serum level of GGT was positively associated with an increased risk of CKD in Iraqi adults but not ALT and AST. Similarly, Souza *et al.*[18] reported that the levels of GGT in a cohort of 87 CKD patients undergoing dialysis therapy were higher than the ALT and AST levels. At the same time, Postorino *et al.*[19] reported a strong association between high levels of GGT in a cohort of 584 CKD patients on peritoneal dialysis. Consistently, Yilmaz *et al.*[6] noted that CKD patients

showed an elevation in the serum activity of GGT in association with endothelial dysfunction. Two recent studies by Torino *et al.*[13] and by Caravaca-Fontan *et al.*[13] reported that the serum GGT levels were high in end-stage kidney dialysis patients, which were perfectly consistent with our results. Collectively, these investigations indicated that the GGT levels were elevated in CKD patients without the elevation of other liver enzymes. On the contrary, Rekha and Murthy[12] revealed that the serum level of GGT was negatively associated with patients with CKD. Moreover, other groups of investigators reported that the serum levels of GGT, ALT and AST were decreased near the lower end of the normal range values in CKD patients for reasons that still haven't been identified[5,6,12]. In 2014, Sette and Almeida Lopes[20] concluded that there were no statistically significant differences between CKD patients and the controls with regard to the levels of the serum GGT, ALT and AST. However, none of these previous studies looked into the causes for the observed variation in the levels of GGT, ALT and AST. Nonetheless, the observed variations between these studies could be related to the methodology, the genetic makeup of the selected population, the size of the examined sample, the duration of CKD, the availability and reliability of the collected data and/or other unknown environmental factors. These factors may ultimately impact or affect the interpretation of the obtained results.

It has been reported that CKD may exist together with other conditions such as cardiovascular disease, diabetes mellitus, hypertension and obesity[5,21]. Interestingly, some previous studies revealed that high GGT level may be related to the presence of some comorbidities especially liver diseases, bile duct damage, type II diabetes mellitus, heart failure and other cardiovascular diseases, malnutrition-inflammation-atherosclerosis and mortality from all causes[5,10-14,19]. These studies also reported that the GGT level increased earlier than the ALT and AST levels and persists longer. In addition, Liberato *et al.*[5] found that the GGT level was slightly higher in HD patients compared with patients who were undergoing peritoneal dialysis. They also observed that the GGT level before HD session was significantly lower than that after HD session, suggesting that this reduction in the GGT level may be due to hemodilution. Later, Alkozai *et al.*[10] revealed that individuals with CKD were more likely to have chronic liver diseases during HD. Very recently, Caravaca-Fontan *et al.*[13] noted that the GGT levels in patients undergoing chronic dialysis therapy may be elevated due to use of prescription and over-the-counter medicine. At the same time, it was reported that the abnormally elevated serum GGT levels were independent predictors of mortality in patients with CKD[13]. Collectively, these studies indicated that an elevation of the GGT level can be considered as an early predictive marker for the development of various diseases, including CKD. In the present study, none of the control participants and CKD patients showed any signs or symptoms of liver diseases at the time of the study. In addition, serum ALT and AST as a marker of liver diseases did not increase in CKD patients compared to the control group and remained within the normal reference range, which may rule out any liver diseases. These data suggested that association between the elevated GGT level and risk of CKD may not related to liver disease. However, it cannot be assured that the high GGT level was mainly due to CKD. As noted above, the elevated serum GGT level had been seen in various diseases and the diagnosis of other diseases did not adequately address in our patients. For the future investigation, screen CKD patients for some diseases including prediabetic conditions or diabetes mellitus and other diseases must be carried out.

Furthermore, the GGT level was slightly higher in males with CKD compared with that in females with CKD. Based on previous studies, males and females have similar levels, although some studies have shown an elevation of the GGT level in males compared with female[22-25]. An interesting observation from this study is that the serum GGT levels for both CKD patients and the controls were significantly higher among cases who were less than 40 years old, obese or smoker but not among those cases older than 40 years old, non-smokers and having normal body weight. It is well-known that cigarette smoking and obesity are risk factors for various diseases including CKD[26-29]. In accordance with our results, two previous studies concluded that obese subjects were more likely to have elevated serum GGT level when compared to normal weight subjects[30,31]. A positive correlation between smoking and the incidence of CKD has been previously documented[32-35]. Caravaca-Fontan *et al.*[13] observed higher values of the serum GGT levels in the smokers than in nonsmokers. Ryu *et al.*[25] also reported that the risk of CKD was significantly associated with the serum level of GGT and variables such as smoking, age and BMI showed positive relationships with serum GGT concentrations in CKD patients. Later, a study by Noborisaka[34] suggested that high level of the serum GGT in smokers might be implicated in the development of CKD. A recent prospective observational study revealed that the level of serum GGT was found to be associated with increased risk of CKD and the increased rate was independent of age, BMI, alcohol drinking and other diseases such as diabetes mellitus, hypertension, hypertriglyceridemia and metabolic syndrome[36]. Similarly, this present study showed a significant association between the serum GGT level and CKD patients regardless of gender, age,

BMI and smoking status. Taken together, these findings supported the notion of the use of the serum GGT level as a reliable biomarker for CKD for the general population. However, due to the low specificity and the fact that an elevation of the GGT level was associated with various diseases may limit the use of the GGT level as a reliable biomarker for CKD.

The combined risk of smoking and the elevated level of GGT on the development of CKD has been reported[34]. The combined effects of age, hypertension and smoking were also observed in the risk of CKD[35]. These findings high light the importance of the combined risk of smoking, obesity and high serum concentrations of GGT on the development of high risk CKD. Unfortunately, due to the size of the sample and the nature of study as well as the lack of clinical data, we were unable to assess the combined effects of smoking, age and BMI in the examined CKD patients.

Even though there was an association between the GGT level and risk of CKD, the physiological significance of GGT by which the elevated GGT level is associated with the development of CKD has not been clarified sufficiently yet due to the complexity of biological processes of CKD[5,13,14,21]. Using the existing data about the GGT function, it is possible to suggest that the association of the elevated serum GGT with the risk of developing CKD may be related to the oxidative stress[19,24,37]. In favor of this hypothesis, a growing body of evidence has been accumulated regarding the interfering role of the oxidative stress in many chronic diseases processes including CKD from both experimental and human studies during the last two decades[6,24,37-40]. Based on these studies, oxidative stress commonly caused by an imbalance between free radical production and antioxidant defense in the human body. Normally, the human body uses antioxidant substances to scavenge free radicals and reduced oxidative stress effects. One of these antioxidants is glutathione[41-43]. It is the most abundant antioxidant in the human body that is capable to minimize oxidative damage. Interestingly, GGT has also been linked with oxidative stress[19,22,24,25]. GGT is primarily found in the liver, kidney and other organs but it is also present in small amount in many organs and tissue throughout the body[19,22]. GGT is also known to catalyze extracellular reduced glutathione, resulting in the formation of cysteinylglycine[40,43]. In fact, this product can react with iron which resulted in the production of superoxide (reactive oxygen species). Therefore, elevation of GGT level had been linked to lower the levels of intracellular glutathione and increase reactive oxygen species inside the human body.

The present study had a series of limitations. The main limitation of this present investigation was that it was performed on a small number of controls and CKD patients at a single center. This small sample size may lead to inefficient analysis. Another major limitation was associated with the limited ability to carry out advanced investigations in terrible areas such as Iraq. There were limitations associated with limited fund to recruit more control and patient participants and the lack of some data for some variables, because of non-response. For instance, the combined effects of age, smoking and BMI should be taken into consideration when analyzing the association between the elevated GGT level and risk of CKD. Absence or lack of such data or analyses may affect the interpretation of the results of this current study.

Despite the fact that the results from Iraq population might not be representative of other races, however, these findings are novel and significant in this population. Moreover, the current study supports the previous observations regarding the association between the GGT level and risk of CKD. The study also revealed the importance of age, BMI and smoking status on the serum GGT level, hence the influence of these factors should be taken into consideration when investigated the association between the serum level of GGT and risk of CKD.

CONCLUSION

The present study demonstrated that an elevation of the serum GGT level was associated with risk of having CKD in a case-control study in the middle-aged and elderly in Iraqi people, regardless of age, gender, BMI and smoking status. In addition, the serum ALT and AST levels remained closely similar in the controls and patients with CKD.

The results of this study also revealed that high BMI and cigarette smoking were two important modifiable risk factors for the elevation of the serum GGT level in CKD patients. These findings raise the importance of maintaining a healthy weight and smoking cessation to decrease the serum GGT level to the normal, which might reduce the risk and incidence of CKD and other related diseases. Although the current study only addressed the effects of these two factors separately on the serum level of GGT, the combined effects of high BMI and consumption of cigarette on the serum GGT levels in both the healthy controls and patient subjects with CKD may be deserving further exploration.

SIGNIFICANCE STATEMENT

This study described the discovery of the association between serum GGT level and CKD that can be beneficial for early recognition of CKD. The findings of this study will be the

driving force to investigate the role of GGT in CKD. Also, this discovery will help investigators to lay a new foundation for future research and uncover the critical areas of early detection and treatment of CKD that several investigators were unable to explore. Thus, a new theory about the potential role and/or the molecular pathomechanism of the GGT in CKD may be discovered and an appropriate therapy to improve the quality of life in CKD patients may be arrived at.

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