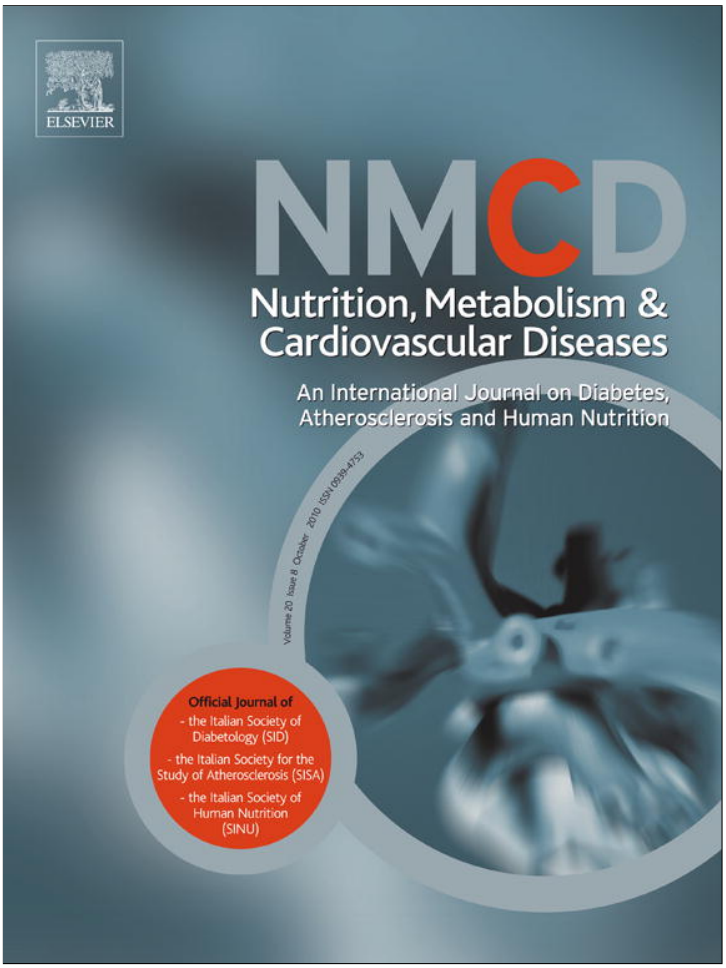

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Relationship between serum gamma-glutamyltransferase and chronic kidney disease in the United States adult population. Findings from the National Health and Nutrition Examination Survey 2001–2006

G. Targher [a,*], J. Kendrick [b], G. Smits [b], M. Chonchol [b]

[a] *Section of Endocrinology, Department of Biomedical and Surgical Sciences, University of Verona, Ospedale Civile Maggiore, Piazzale Stefani 1, 37126 Verona, Italy*
[b] *Division of Renal Diseases and Hypertension, University of Colorado Denver Health Sciences Center, Denver, CO, USA*

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KEYWORDS
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Abstract *Background and aims:* Elevated serum levels of gamma-glutamyltransferase (GGT) are a marker of liver injury, but may also be associated with other diseases and death. Currently, the association of serum GGT concentrations with chronic kidney disease has not been established in the U.S. general population.
Methods and results: We performed a cross-sectional analysis of data from the National Health and Nutrition Examination Survey 2001 through 2006 and examined the association between serum GGT concentrations and chronic kidney disease in a nationally representative sample of 13,188 adults aged 20 years or older. Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease formula. The prevalence of chronic kidney disease defined as eGFR <60 ml/min/1.73 m^2 or abnormal albuminuria in those with eGFR ≥ 60 ml/min/1.73 m^2 was 13.9% ($n = 1842$). Serum GGT elevation was associated with an increased odds of chronic kidney disease (odds ratio 2.38, 95% confidence intervals 2.02–2.80, $p < 0.0001$). After adjustment for demographics, comorbidities, daily alcohol consumption, lipid-lowering medications, viral hepatitis status and laboratory measures, the odds ratio of chronic kidney disease per log serum GGT increase was 1.79 (1.41, 2.27; $p < 0.0001$).
Conclusions: These results show a strong, independent, relationship of increased serum GGT concentrations with chronic kidney disease in the US adult population.

* Corresponding author. Tel.: +39 045 8123748; fax: +39 045 8027314.
E-mail address: giovanni.targher@univr.it (G. Targher).

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Introduction

Chronic kidney disease (CKD) is now recognized as a common condition that markedly increases the risk of cardiovascular disease, end-stage renal disease and other comorbidities. The number of patients with end-stage renal disease is increasing and represents a major public health problem worldwide [1—7]. Because kidney disease often progresses to kidney failure with its attendant complications, the identification of precursors and risk factors for CKD are essential, with the belief that interventions will prevent or delay progression to kidney failure.

Elevated concentrations of serum gamma-glutamyltransferase (GGT) have long been used as a reliable index of alcohol abuse and liver dysfunction. Serum GGT has been recently proposed as a marker of oxidative stress [8,9]. In addition, several population-based studies have found strong, positive, associations of serum GGT concentrations, within the reference range, with future risk for all-cause mortality, major cardiovascular events and diabetes, independently of alcohol intake and other prognostic factors [10—15]. Recently, mildly elevated serum GGT concentrations also predicted cardiovascular and all-cause mortality in patients with end-stage renal disease [16], and incident CKD in a cohort of healthy Asian male workers [17].

To our knowledge, the association between serum GGT concentrations and CKD has not been established in the US general population. Thus, the aim of this study was to assess the association between serum GGT concentrations and CKD in a nationally representative sample of the US adult population.

Methods

Study population

The National Health and Nutrition Examination Surveys (NHANES) are cross-sectional probability samples designed to obtain information on health and nutritional status of the US civilian non-institutionalized population conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention [18]. The NHANES examinations were conducted from 2001 to 2006 in three phases (2001—2002, 2003—2004 and 2005—2006), and data from these phases were combined for the purpose of this analysis, following NCHS analytic guidelines [19]. The NCHS institutional review board approved the NHANES protocols. Informed consent was obtained from all participants [20].

In all NHANES, a stratified, multistage sampling design was used, with over-sampling of non-Hispanic blacks, Mexican—Americans and persons over the age of 60 years. Standardized questionnaires were administered at home, followed by a detailed physical examination and blood specimens at a mobile examination center [18]. This analysis was initially restricted to 13,217 adults of 20 years or older. However, responders who had a missing serum GGT and incomplete data for the calculation of eGFR by the Modification of Diet in Renal Disease (MDRD) formula [21] or had an eGFR <15 mL/min/1.73 m^2 were excluded from analysis ($n = 29$). Individuals with eGFR <15 mL/min/1.73 m^2 were excluded due to the small number of participants and the likelihood that many of these individuals were receiving dialysis. Thus, the final sample used in this study included 13,188 adults.

Study variables

The independent variable of interest was GGT. Serum GGT concentrations were measured on a Beckman Synchron LX20 performed by the central laboratory that underwent regular internal and external quality control procedures. A detailed description of the laboratory assays and quality control procedures is available elsewhere [18—20]. On the basis of the NHANES 2001—2006 laboratory cut-off values for normal levels, serum GGT higher than 65 U/L for men and 36 U/L for women were considered abnormal. The lower limit of detection was 5.0 U/L, and pooled controls had a coefficient of variation between 1.1% and 6.7% [18—20].

The primary dependent variable of interest was the presence of CKD defined as eGFR <60 ml/min/1.73 m^2 or abnormal albuminuria (i.e., microalbuminuria or macroalbuminuria) [21]. eGFR values were derived from the re-expressed MDRD Study formula $= 175.0 \times (\text{serum creatinine value})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.21$ (if black) [21]. Values that exceeded 200 ml/min/1.73 m^2 were truncated to that level. Serum creatinine was measured using the Jaffé method (kinetic alkaline picrate) [18—20,22]. As recommended by NHANES analytic guidelines [22], NHANES serum creatinine values in 2005 through 2006 were adjusted to ensure comparability with standard creatinine using the following formula: standard creatinine (mg/dl) $= -0.016 + 0.978 \times$ (NHANES 2005 through 2006 un-calibrated serum creatinine [mg/dl]). No adjustment was needed for serum creatinine levels measured in 2001 through 2004 [22,23]. Urinary albumin excretion was measured by a fluorescent immunoassay (Sequoia-Turner model 450 digital fluorometer) on the basis of the spot urine albumin/creatinine ratio. Abnormal albuminuria was defined as urinary albumin/creatinine ratio ≥ 30 mg/g [21].

Serum total cholesterol, HDL cholesterol and triglycerides were measured enzymatically with a Hitachi-704 Analyzer (Roche Diagnostics, Indianapolis, USA). LDL-cholesterol was calculated using the Friedewald's equation, except in those with triglycerides exceeding 4.54 mmol/l. Plasma glucose was measured by a modified hexokinase enzymatic method, and a separate radioimmunoassay method was used to measure serum insulin [18]. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using fasting glucose and insulin measurements: [(fasting insulin (μU/mL) $\times$ fasting glucose (mmol/l))/22.5] [24]. HOMA-IR was available only in those without known diabetes ($n = 5633$). Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured on a Beckman Synchron LX20 employing the alpha-ketoglutarate reaction. Exposure to hepatitis C virus (HCV) was determined by presence of antibody to HCV, and hepatitis B infection was identified by having a positive hepatitis B core antibody serology [18].

Questionnaire data included self-reported age and gender. Age was stratified into groups: 20—39, 40—59, 60—69 and ≥ 70 years. Race/ethnicity was grouped into four categories: non-Hispanic white, non-Hispanic black, Mexican—

American and other. Smoking status was classified as never smoker, ex-smoker and current smoker. Alcohol consumption was recorded as number of drinks per day. Hypertension was diagnosed if the participant was taking anti-hypertensive medications, reported being told by a physician that they have high blood pressure, or the average of three blood pressure readings was $\geq$140/90 mmHg. Participants were defined as having diabetes when they were taking hypoglycaemic drugs, had a fasting plasma glucose concentration $\geq$7.0 mmol/l or when a physician had ever told them that they had diabetes. Participants who answered yes to the question ''Are you taking any medications to lower your high cholesterol?'' were analyzed as receiving lipid-lowering medications [18]. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured with a steel measuring tape to the nearest 0.1 cm at the high point of the iliac crest at minimal respiration [18].

Statistical analysis

GGT was analyzed by dividing its distribution into quartiles. Cut-points for sex-specific quartiles were defined based on the GGT distribution of all participants at baseline. Cross-sectional associations of serum GGT quartiles with baseline demographics and risk factors were performed using the chi-square test for discrete variables and the one-way analysis of variance for continuous variables (Table 1). The independent association of serum GGT with CKD was investigated using logistic regression analysis, adjusting simultaneously for potential confounders. In the whole cohort (Table 2), the covariates included in fully-adjusted regression models were: age, gender, race/ethnicity, smoking history, alcohol consumption, lipid-lowering medications, hypertension, diabetes, BMI, waist circumference, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, ALT, AST, and viral hepatitis status. Multivariate regression models including HOMA-IR score as an additional covariate were restricted to those without diagnosed diabetes ($n = 5633$) (Table 3). In all of these analyses, GGT was modelled as a continuous variable or by quartile. Because of skewness of its distribution, GGT was logarithmically transformed for statistical analysis. The distributions of serum triglycerides, AST, ALT and HOMA-IR were skewed, and were also log-transformed. As obesity is an important potential confounder, BMI and waist circumference were included as linear or non-linear covariates yielding identical results. In all logistic regression models, observations were weighted to reflect the general US population as of early 2000s, using weights calculated for that purpose by the National Health Statistics [19]. Analyses were conducted using SAS-callable SUDAAN statistical software (Research Triangle Institute, Research Triangle Park, NC). p Values <0.05 were considered statistically significant.

Results

Among the 13,188 participants, abnormal serum GGT concentrations were present in 9.3% of men (i.e., GGT $>$65 U/L) and 11.7% of women (GGT $>$36 U/L), respectively. In addition, CKD defined as eGFR $<$60 ml/min/1.73 m^2 or abnormal albuminuria in those with eGFR $\geq$ 60 ml/min/1.73 m^2 was present in 13.9% ($n = 1842$) of the whole sample.

The clinical characteristics of participants stratified by sex-specific serum GGT quartiles are shown in Table 1. Compared with participants with normal GGT, those with higher serum GGT levels were older, more centrally obese, more likely to be non-Hispanic black or Mexican–American, to be smoker, to be heavier drinkers, and had higher serum ALT and AST concentrations, and greater prevalence of hypertension, diabetes, dyslipidemia and seropositivity for viral hepatitis B or C. They also reported lipid-lowering medications more frequently, but did not differ significantly with regard to sex compared to those with normal GGT levels. Notably, persons with higher serum GGT levels also had a greater frequency of CKD (as defined above) or abnormal albuminuria alone (i.e., albumin/creatinine ratio $\geq$30 mg/g irrespective of eGFR).

Table 2 shows the association between GGT and CKD in both unadjusted and fully adjusted regression models. Elevated GGT was associated with increased odds of CKD in unadjusted models. After adjustment for demographics, comorbidities, alcohol consumption, viral hepatitis status and laboratory measures, the odds ratio of CKD per unit increase of log GGT was 1.79 (95% confidence intervals 1.41–2.27; $p < 0.0001$). As shown in Table 2, when GGT was included as a categorical measure in multivariate regression models, it appeared that there was a stepwise increase in the rate of CKD across GGT quartiles that was more prominent among those in the top quartile, independently of known risk factors and other potential confounders.

Similarly, the association between serum log GGT and CKD remained statistically significant (odds ratio 1.85, 95% confidence intervals 1.31–2.63, $p < 0.0001$) even when adjustment was made for the presence of the metabolic syndrome (as defined by the updated Adult Treatment Panel III criteria), which was included as a categorical variable in the fully adjusted regression model instead of all its individual components.

We conducted sensitivity analyses to evaluate the robustness of our findings. Almost identical results were found when the results were stratified by gender (Fig. 1) or when the associations between GGT and each renal outcome (i.e., eGFR and albuminuria) were evaluated separately in parallel regression models ($p < 0.0001$ for both; data not shown). When we performed a subgroup analysis of participants stratified by age groups (20–39, 40–59, 60–69 and $\geq$70 years), the relationship between serum GGT and CKD remained statistically significant ($p < 0.0001$ for all) in all age groups – both in unadjusted and adjusted regression analysis – except in participants older than 70 years (data not shown). Finally, in analysis limited to persons without known diabetes, elevated serum GGT was associated with an 86% higher risk of prevalent CKD in the fully adjusted regression model (Table 3). In this analysis, we adjusted for the same set of the above covariates plus HOMA-estimated insulin resistance.

Discussion

In recent years, our knowledge of the physiological functions of GGT has expanded and several important

Table 1 Clinical characteristics of participants by sex-specific serum GGT quartiles ($n = 13,188$).

Sex-specific GGT quartiles	Q1	Q2	Q3	Q4	*p*-Value for trend
	Men 5–17, women 3–11	Men 18–25, women 12–16	Men 26–38, women 17–24	Men >39 U/L, women >25 U/L	
GGT (U/L)*	11 [9, 14]	16 [14, 21]	24 [19, 30]	46 [35, 68]	
n	3151	3636	3218	3183	
Age in years (%)					<0.0001
20–39	56.4	46.0	37.5	32.0	
40–59	26.5	32.0	38.2	44.7	
60–69	6.5	10.0	12.0	12.7	
≥70	10.6	12.0	12.3	10.6	
Gender (%)					0.44
Males	48.2	47.4	46.2	47.6	
Females	51.8	52.6	53.8	52.4	
Ethnicity (%)					<0.0001
Non-hispanic white	59.2	52.7	47.5	42.9	
Non-hispanic black	14.1	18.4	24.5	25.1	
Mexican–American	22.6	24.3	24.1	28.5	
Other	4.1	4.6	3.9	3.5	
Smoking status (%)					<0.0001
Never	58.0	54.9	50.7	46.0	
Former	22.0	22.7	24.5	23.8	
Current	20.0	22.4	24.8	30.2	
Alcohol drinks per day (%)					<0.0001
0	26.8	26.0	27.2	25.3	
1–3	60.3	60.6	57.5	53.7	
>3	12.9	13.4	15.3	21.0	
Hypertension (%)	18.3	24.1	32.4	36.6	<0.0001
Diabetes (%)	4.9	6.6	9.4	11.9	<0.0001
Chronic kidney disease (%)	10.9	11.8	14.9	18.5	<0.0001
Medication use					
Lipid-lowering medications (%)	5.1	6.4	8.7	8.5	<0.0001
Measurements					
Body mass index (kg/m^2) (%)					<0.0001
<25	47.7	35.4	23.5	19.0	
25–29	33.9	35.1	36.1	35.0	
≥30	18.4	29.5	40.4	46.0	
Waist circumference (cm)	92 ± 14	96 ± 16	100 ± 16	102 ± 16	<0.0001
Glucose, mmol/l (%)					<0.0001
<6.11	93.2	90.4	86	80.2	
6.11–6.99	3.5	4.9	6.1	7.6	
≥7.0	3.3	4.7	7.9	12.2	
Total Cholesterol, mmol/l (%)					<0.0001
<5.12	59.3	53.7	47.9	43.1	
5.12–6.15	26.2	31.6	33.8	34.2	
>6.15	14.5	14.7	18.3	22.7	
LDL cholesterol, mmol/l (%)					<0.0001
<3.33	71.6	67.2	63.1	60.9	
3.33–4.10	19.2	20.9	23	23.9	
>4.10	9.2	11.9	13.9	15.2	
HDL cholesterol, mmol/l (%)					<0.0001
>1.54	36.9	30.7	25.1	24.5	

Table 1 (*continued*)

Sex-specific GGT quartiles	Q1	Q2	Q3	Q4	*p*-Value for trend
	Men 5–17, women 3–11	Men 18–25, women 12–16	Men 26–38, women 17–24	Men >39 U/L, women >25 U/L	
GGT (U/L)*	11 [9, 14]	16 [14, 21]	24 [19, 30]	46 [35, 68]	
0.90–1.54	58.3	62.9	66.2	65.9	
<0.90	4.8	6.4	8.7	9.6	
Triglycerides, mmol/l (%)					<0.0001
<1.76	77.3	72.1	64.2	51.4	
≥1.76	22.7	27.9	35.8	48.6	
AST, units/l	22 ± 12.7	23.1 ± 15.1	24.5 ± 9.3	31.6 ± 29.4	<0.0001
ALT, units/l	18.9 ± 8.1	21.8 ± 10.8	25.6 ± 13.5	36.6 ± 35.7	<0.0001
HOMA-IR score*	1.5 [1.0, 2.3]	2.0 [1.3, 3.1]	2.6 [1.5, 4.3]	3.4 [1.9, 5.6]	<0.0001
Abnormal albuminuria (%)	7.6	7.7	11.1	14.4	<0.0001
Hepatitis B antibody (%)	20.0	19.7	17.2	16.3	<0.0001
Hepatitis C antibody (%)	0.4	0.4	0.5	2.5	<0.0001

Data are expressed as means ± SD, percentages or *medians [inter-quartile range].
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; and HOMA-IR = homeostasis model assessment of insulin resistance which was available in non-diabetics only ($n = 5633$).

epidemiological associations have been reported. Numerous population-based studies have found strong, positive, associations of serum GGT concentrations with the risk of all-cause mortality, major cardiovascular events and type 2 diabetes, independently of traditional risk factors and alcohol consumption [10–15].

To our knowledge, this is the first large population-based study specifically aimed at assessing the association between serum GGT concentrations and CKD in the US general population. Our results indicate that elevated serum GGT concentrations, within the reference range, are consistently associated with an increased prevalence of CKD in US adults. Notably, this association is independent of a wide range of known risk factors and potential confounders, such as age, gender, race/ethnicity, smoking, hypertension, diabetes, body mass index, waist circumference, plasma lipids, glucose, insulin resistance, aminotransferases, viral hepatitis status, lipid-lowering medications, and daily alcohol consumption.

Currently, the information on the association between serum GGT concentrations and CKD is scarce. Our findings are corroborated by a recent prospective study of 10,337 non-hypertensive and non-diabetic Korean male workers followed for ~3.5 years, demonstrating that mildly

Table 2 Cross-sectional association between sex-specific serum GGT levels and chronic kidney disease in the whole cohort ($n = 13,188$).

	Log GGT	Sex-specific serum GGT quartiles			
		Q11	Q2	Q3	Q4
		Men 5–17, women 3–1	Men 18–25, women 12–16	Men 26–38, women 17–24	Men >39 U/L, women >25 U/L
Unadjusted OR (95% CI)	2.38 (2.02, 2.80), $p < 0.0001$	1.00 (ref)	1.10 (0.94, 1.27), $p = 0.25$	1.42 (1.23, 1.65), $p < 0.0001$	1.85 (1.61, 2.14), $p < 0.0001$
Adjusted OR (95% CI)[a]	1.80 (1.42, 2.28), $p < 0.0001$	1.00 (ref)	0.97 (0.81, 1.15), $p = 0.68$	1.11 (0.93, 1.33), $p = 0.25$	1.43 (1.18, 1.73), $p = 0.0003$
Adjusted OR (95% CI)[b]	1.79 (1.41, 2.27), $p < 0.0001$	1.00 (ref)	0.97 (0.82, 1.15), $p = 0.73$	1.12 (0.94, 1.34), $p = 0.22$	1.44 (1.19, 1.74), $p = 0.0002$

Data are odds ratios (OR) and 95% confidence intervals (CI). Gamma-glutamyltransferase (GGT) has been logarithmically transformed before analysis.
[a] Adjusted for age, gender, race/ethnicity, smoking, hypertension, diabetes, lipid-lowering medications, body mass index, waist circumference, glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, alanine aminotransferase and aspartate aminotransferase.
[b] Additionally adjusted for alcohol consumption and seropositivity for viral hepatitis B or C.

Table 3 Cross-sectional association between serum GGT levels and chronic kidney disease in non-diabetic individuals ($n = 5633$).

	Log GGT
Unadjusted OR (95% CI)	1.44 (1.20, 1.73), $p < 0.0001$
Adjusted OR (95% CI)[a]	1.86 (1.26, 2.73), $p = 0.002$

Data odds ratios (OR) and 95% confidence intervals (CI). Gamma-glutamyltransferase (GGT) has been logarithmically transformed before analysis.

[a] Adjusted for age, gender, race/ethnicity, smoking, hypertension, lipid-lowering medications, body mass index, waist circumference, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, alcohol consumption, viral hepatitis B or C markers and HOMA-IR score.

elevated serum GGT concentrations predicted the development of incident CKD (defined as eGFR <60 ml/min/1.73 m^2 or albuminuria) independently of age, baseline eGFR, metabolic syndrome features, C-reactive protein, smoking, and alcohol intake [17].

Clearly, we must be cautious in making any causal inference, given the cross-sectional design of our study. The underlying mechanism(s) by which elevated serum GGT levels may contribute to increased risk of CKD are poorly understood. The most obvious explanation for our findings is that the greater prevalence of CKD in persons with higher serum GGT concentrations simply reflects the coexistence of underlying known risk factors. However, since in our study higher serum GGT levels were associated with higher CKD rates independently of a broad spectrum of known risk factors, it is conceivable that serum GGT might confer an excess risk over and above the risk expected as a result of the underlying established risk factors. In clinical practice, an

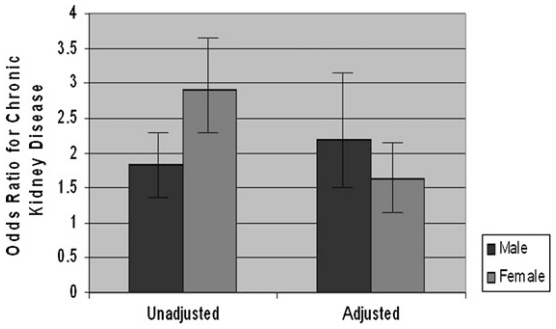

Figure 1 Association between serum log GGT concentrations and chronic kidney disease among 13,188 adult participants stratified by gender. Data are odds ratios and 95% confidence intervals by logistic regression analysis, both unadjusted and adjusted for age, race/ethnicity, smoking, hypertension, lipid-lowering medications, body mass index, waist circumference, plasma lipids, glucose, AST, ALT, alcohol consumption, and viral hepatitis markers. All results are significant at $p < 0.001$ or less.

increased serum GGT concentration is conventionally interpreted as a marker of alcohol abuse and liver dysfunction [10–15]. In our study, however, elevated GGT levels were associated with higher CKD rates even after adjusting for alcohol consumption and viral hepatitis markers. Thus, viral hepatitis and alcohol consumption are unlikely to fully explain the association of serum GGT with CKD.

A possible underlying mechanism linking serum GGT and CKD risk could be the presence of non-alcoholic fatty liver disease (NAFLD). Mildly elevated serum GGT levels are considered a reliable marker of NAFLD and are associated with higher liver fat content [25,26]. NAFLD is now regarded as the hepatic manifestation of the metabolic syndrome and represents the most common cause of abnormal serum liver enzymes in Western countries, affecting up to a third of the general population [25,26]. Although, in our study, the relationship between serum GGT levels and CKD was independent of the metabolic syndrome components, however, NAFLD per se might actively contribute to pathogenesis of CKD – as well as to accelerated atherogenesis – through the release of some pathogenetic mediators from the steatotic/inflamed liver, including increased reactive oxygen species, elevated C-reactive protein and other pro-inflammatory cytokines [27]. Importantly, several studies have shown that these potential mediators of vascular and renal injury are remarkably higher in patients with NAFLD than in those without [28–31], and are thought to be pathogenic factors for the development of CKD [32–34]. Consistent with the hypothesis that liver inflammation (or other liver-derived factors) in NAFLD may play a role in the CKD progression, Cheng et al. reported that in a type 2 diabetic population, those with chronic hepatitis B virus infection were more likely to develop end-stage renal disease than those not infected with hepatitis B virus [35]. Finally, and more importantly, recent studies have demonstrated that ultrasound-diagnosed NAFLD was strongly associated with increased risk of CKD in non-diabetic and diabetic populations independently of metabolic syndrome and other established risk factors [36–38].

Oxidative stress, both localized within atherosclerotic plaques and systemic, may also link GGT with CKD. GGT is present in atherosclerotic plaques and may catalyze oxidation of LDL lipoproteins and thereby contribute to plaque evolution and rupture [8,9,12,13]. GGT is also present on the surface of most cell types and is the enzyme responsible for the extracellular catabolism of antioxidant glutathione. Ectoplasmic GGT has been implicated in the generation of reactive oxygen species, and consistent evidence supports its role as a marker of systemic oxidative stress [8,9]. In light of the evidence that oxidative stress plays a role in the pathophysiology of renal damage [32–34], it is also possible to hypothesize that the relationship of GGT to oxidative stress may be another potential explanation for the association of serum GGT levels with CKD. This conclusion is indirectly supported also by the results of our multivariate regression analyses showing a strong, graded, association between serum GGT levels and CKD after adjustment for serum aminotransferases, which are considered markers of liver injury but not of systemic oxidative stress. However, we cannot *a priori* exclude the possibility of reverse causality (i.e., CKD causing

higher serum levels of GGT). While oxidative stress has been hypothesized to cause CKD, it has also been hypothesized that CKD causes oxidized stress (and that this is one mechanism through which CKD leads to higher serum GGT levels) [21].

Therefore, a central question still remains: why should serum GGT increase in CKD? This question, however, applies also to all epidemiological studies describing independent associations between elevated serum GGT levels and cardiovascular morbidity and mortality in the general population [10—15]. Still, GGT activity remains a non-specific laboratory test. A recent study performed a new laboratory method based on gel filtration chromatography, which permitted the quantification of four GGT fractions of different molecular weight in plasma of healthy volunteers [39]. Plasma GGT fraction analysis could improve the low specificity of current GGT assay, thus also contributing to better understand the complex links between this enzyme and adverse clinical outcomes.

This study has some important limitations that merit comment. First, the cross-sectional design of the study precludes the establishment of causal or temporal relationships between serum GGT and CKD. Second, liver ultrasonography for diagnosing NAFLD was not performed. Third, we used an eGFR instead of a directly measured GFR to define CKD. It is known that current GFR estimates have greater inaccuracy in populations without known CKD than in those with kidney disease. Nonetheless, current GFR estimates facilitate the detection, evaluation, and management of CKD, and many organizations recommend the use of prediction equations for the evaluation of kidney function in large epidemiologic studies and in clinical practice [21].

Despite these limitations, our analysis has several important strengths. First, it is the most comprehensive national survey to estimate the association between serum GGT and prevalent CKD in US adults. Second, NHANES used uniform methods to collect data on demographics, comorbidities and laboratory measures. Third, the extensive and complete data on important factors associated with CKD and serum GGT elevation, allows us to give an unbiased estimate for the relationship between serum GGT and CKD. Finally, with the design of NHANES, we are able to generalize the results to the entire US civilian non-institutionalized population.

In conclusion, our findings suggest that increasing serum levels of GGT are independently associated with an increasing prevalence of CKD in the US adult population. Further experimental and follow-up studies are needed to confirm these findings and to elucidate the underlying biologic mechanisms before causality can be firmly established.

Disclosures

None of the authors have any conflicts of interest.

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