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Evaluation of Plasma Cystatin C Depending on Physiological Factors in Healthy Iraqi People

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ABSTRACT

Background: *Cystatin C is a small protein formed by nucleated cells, has gained significant attention as a potential test for various health conditions, including cardiovascular diseases and impaired kidney functions. Although existing research on cystatin C levels in different populations, there remains a gap in understanding its variations in healthy Iraqi individuals, particularly concerning gender, age, and body mass index (BMI).* ***Aim****: This study aims to address this gap by evaluating the evolution of plasma cystatin C levels in 180 healthy Iraqi volunteers.* ***Methods****: the samples were categorized based on age, gender, and obesity status.* ***Results****: showed no significant difference (p-value ≤ 0.05) according to gender with the mean value of Cystatin C as 0.8511 pg/ml and 0.7881 pg/ml in male and female groups, respectively. The result showed gradually elevated levels in Cystatin C according to age, when Cystatin C values were 0.6676 ± 0.1918 pg/ml, 0.8339 ± 0.3416 pg/ml, 0.8442 ± 0.3422 pg/ml, 0.8930 ± 0.3471 pg/ml, 1.103 ± 0.3356 pg/ml in 40s, 50s, 60s, 70s, and 80s groups, respectively (p-value ≤ 0.05). Also, the result showed significant differences (p-value ≤ 0.05) in Cystatin C levels according to BMI with mean values of 0.7578 ± 0.1036 pg/ml, 0.7999 ± 0.3176 pg/ml, 0.9218 ± 0.2629 pg/ml, 1.0280 ± 0.4693 pg/ml in normal BMI, overweight, obese, and extremely obese, respectively.* ***Conclusion****: the study concludes that age and BMI significantly influence serum cystatin C levels in healthy people. These findings provide valuable insights into the physiological factors affecting cystatin C levels in the Iraqi population and underscore the need for finding reference values tailored to this specific demographic.*

Keywords: Age; Cystatin C; Gender; Kidney Disease; Obesity.

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INTRODUCTION

Cystatin C is a nonglycosylated, small protein that is synthesized by nucleated cells in the body and excreted through glomerular filtration[1]. Cystatin C has a molecular weight of 13.4 kDa and is a member of the cystatin superfamily of cysteine protease inhibitors[2]. Cystatin C levels are linked with various infections and diseases. It has been suggested as an effective biomarker for cardiovascular diseases (CVD) [3] and impaired renal function[4]; two prior meta-analyses found an association between elevated serum Cystatin C and a higher risk of incident CVD[5]. It has been previously reported that serum Cystatin C value differs significantly depending on race and ethnicity[6]. In addition, it has been reported that Cystatin C values are different in patients with cancer[7], people who are undergoing therapy with glucocorticoid in some cases[8], and thyroid disorder[9]. Other reports have shown that cigarette smoking can influence the level of C reactive protein and Cystatin C protein[10]. Based on the results of some studies[11–13].

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Previous studies examining the role of gender on cystatin C levels have presented conflicting findings. Whereas some suggest significant gender-based variations, others propose more nuanced differences or even negligible distinctions between males and females [14–16]. Understanding these gender-related differences is critical, as they may have consequences for establishing reference ranges and interpreting cystatin C values exactly. Age, being a fundamental determinant of physiological changes, has been consistently linked to fluctuations in cystatin C levels. The intricate interplay between aging and kidney function has been well-documented [17], highlighting the need for comprehensive evaluations across different age groups. Previous research has indicated that cystatin C concentrations tend to increase proportionally with age, shedding light on potential age-related variations [18].

Body mass index (BMI), an indicator of adiposity, presents another layer of complexity to the relationship with cystatin C level. The link between obesity and renal dysfunction, including chronic kidney disease, has been a subject of growing interest. Obesity-related alterations in hormonal balance, inflammation, and oxidative stress may contribute to changes in cystatin C concentrations, making BMI a relevant factor to explore in the context of cystatin C dynamics [19]. The aim of this study is to investigate the evolution of plasma cystatin C levels in healthy Iraqi individuals, with a specific focus on understanding the influence of gender, age, and body mass index (BMI).

MATERIAL AND METHODS

This cross-sectional study includes 180 healthy volunteers in Samawah City, Iraq. All of them were approved under ethical standards, and all signed consent forms. Criteria for defining healthy volunteers that used in this study including: Absence of chronic diseases, normal laboratory tests (CBC, LFTs, KFTs), Absence of Infections, Medication History. Data information including weight, height, age, gender, and health status were collected. Patients with renal disease, diabetes mellitus, heart disease were excluded from this study.

Study population

The study included 180 healthy volunteers divided according to gender into two groups; the first group consisted of 98 males (54.44%), and the second group consisted of 82 females (45.56%). According to age, the 180 healthy volunteers ranged in age from 43 to 87 years old, and were divided into five groups as follows: 40s (40-49 years old), 50s (50-59 years old), 60s (60-69 years old), 70s (70-79 years old), and 80sS (80-89 years old). BMI (Body Mass Index) categories are defined based on established ranges that are widely accepted in the medical and research community. The commonly used BMI categories are defined by the World Health Organization (WHO) and are as follows: normal BMI (18.5-24.9), overweight (25-29.9), obese (30-34.9), and extremely obese (35< BMI) [20].

Blood collection

Blood samples (3 ml) were collected in EDTA tubes from all healthy volunteers. Plasma was separated using centrifugation at 1600 rpm for 15 min. The plasma was transferred into new plain tubes and kept under refrigeration (−2 °C) until Cystatin C assay[21,22].

Cystatin C assay

Platinum ELISA Cystatin C (Catalog Numbers BMS2279) was used in quantitative detection of human Cystatin C according to enzyme-linked immunosorbent assay, then onto micro-wells, where an antihuman Cystatin C-coated antibody is adsorbed. HRP-conjugated antihuman Cystatin C antibodies were added

which binds to Cystatin C caught by the first antibody, which is Cystatin C present in the sample, or standard connected to antibodies adsorbed by the micro-wells. After incubation, stages of washing removes unbound antihuman Cystatin C HRP-conjugated antibody, and substrate-solution reactive with HRP is added to the wells[23]. Depending on how much Cystatin C is present in the sample or standard, a blue colored product is produced. Acid is added to stop the reaction, and absorbance is then measured at 450 nm. Seven Cystatin C standard dilutions are used to create a standard curve, and the concentration of the Cystatin C sample is determined as in Figure 1.

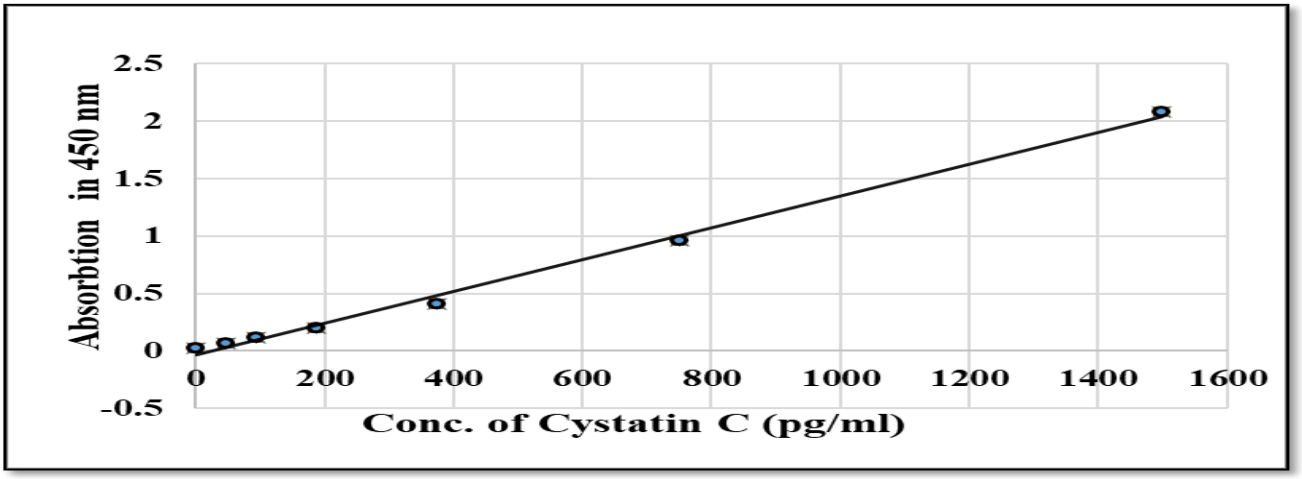

Figure 1: Standard curve of Cystatin C ELISA.

STATISTICAL ANALYSIS

Results were analyzed by GraphPad prism program (Version 6) using ordinary one-way ANOVA and unpaired t-test analysis with a *p-value* of ≤ 0.05. All figures and tables were designed using Microsoft Excel (2020) and GraphPad Prism (Version 6). [24]

RESULTS

Cystatin C concentrations of 180 samples were determined and analyzed according to gender as shown in Figure (2) and Table (1). The result shows the mean value of Cystatin C to be 0.8511 ± 0.02896 pg/ml and 0.7881 ± 0.03893 in male and female groups, respectively. Although there was a difference between both groups, it was considered not to be of any significant difference with a *p* value 0.1877.

The results in Table (1) and Figure (3) show Cystatin C value in 0.6676 ± 0.1918 pg/ml, 0.8339 ± 0.3416 pg/ml, 0.8442 ± 0.3422 pg/ml, 0.8930 ± 0.3471 pg/ml, 1.103 ± 0.3356 pg/ml in 40s, 50s, 60s, 70s, and 80s groups, respectively, and these results show a proportional elevation in Cystatin C value with age with significant difference, and *p* value of 0.0454.

Result analysis of Cystatin C with BMI shown in Figure (4) and Table (1) show result analysis of Cystatin C value with BMI. The mean values of Cystatin C were 0.7578 ± 0.1036 pg/ml, 0.7999 ± 0.3176 pg/ml, 0.9218 ± 0.2629 pg/ml, 1.0280 ± 0.4693 pg/ml in normal BMI , overweight , obese and extremely obese, respectively. The results show a significant increase in Cystatin C value, and proportional increases with weight and *p* value is 0.0226.

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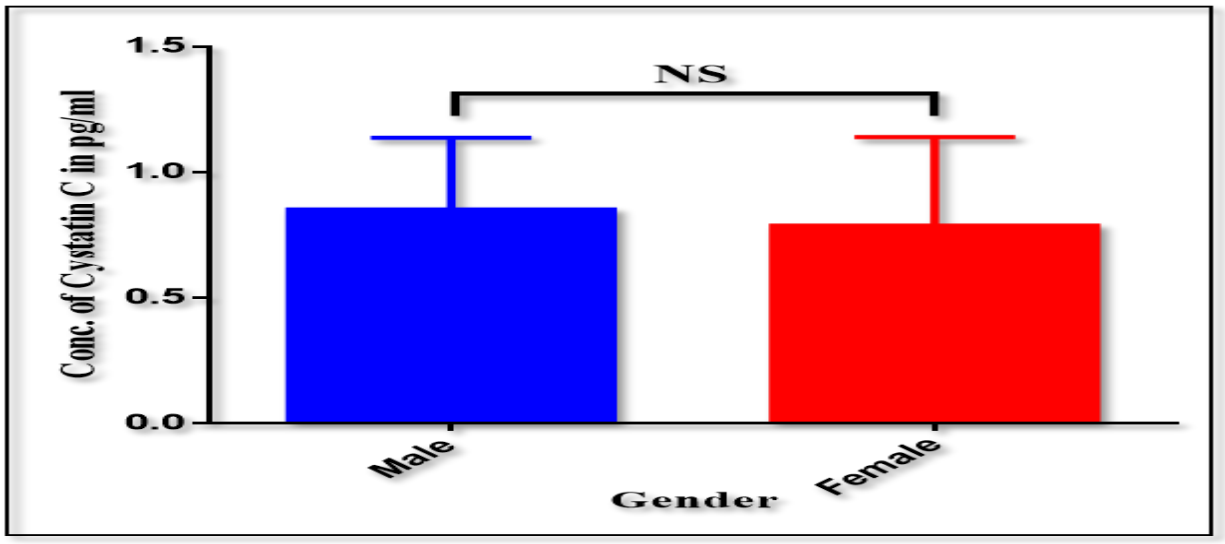

Figure 2: Shows Cystatin C value according to gender groups, *p-value* ≤ 0.05.

Table 1: Results analysis of Cystatin C according to gender, age, and BMI.

Groups	No. of Samples	Mean cystatin C ± SD	*P* value	Minimum	maximum
According to gender					
Male	98	0.8511 ± 0.02896	0.1877	0.2940	1.782
Female	82	0.7881 ± 0.03893	(NS)	0.2190	1.611
According to age (years)					
40 - 49	20	0.6676 ± 0.1918	0.0454 (S*)	0.3370	0.9370
50 - 59	60	0.8339 ± 0.3416		0.2530	1.782
60 – 69	70	0.8442 ± 0.3422		0.2190	1.743
70 - 79	24	0.8930 ± 0.3471		0.4940	1.611
80 - 89	6	1.103 ± 0.3356		0.7270	1.727
According to BMI					
Normal	16	0.7578 ± 0.1036	0.0226 (S*)	0.6446	0.8710
Overweight	118	0.7999 ± 0.3176		0.2190	1.6110
Obese	46	0.9218 ± 0.2629		0.6210	1.5240
Extremely Obese	8	1.0280 ± 0.4693		0.7270	1.7820

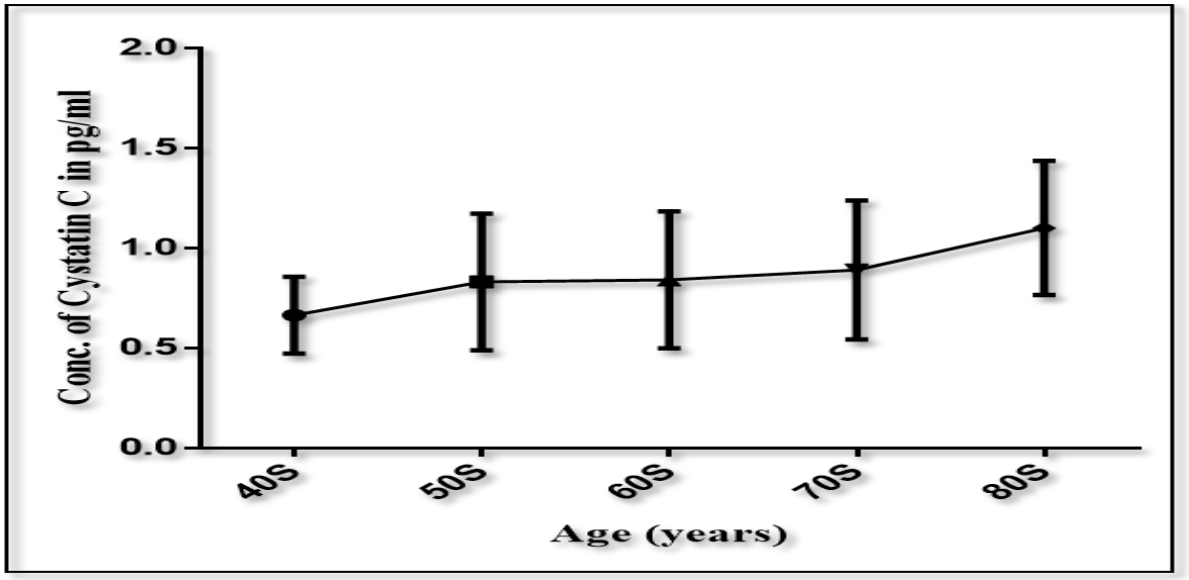

Figure 3: Cystatin C results analysis according to age groups, *p-value* ≤0.05

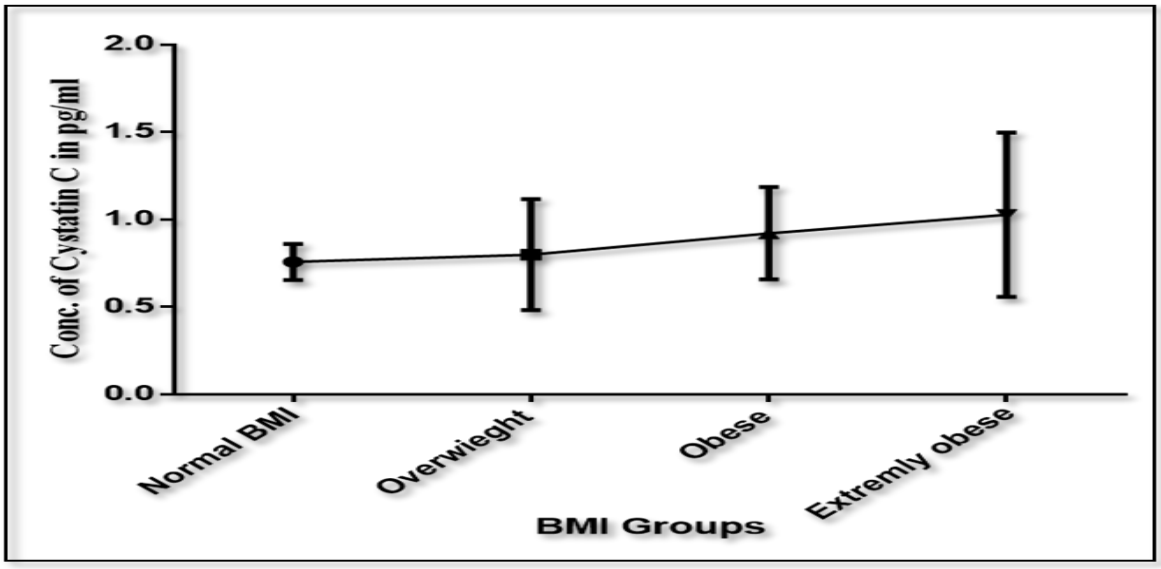

Figure 4: Cystatin C results analysis according to BMI groups, *p-value* ≤0.05

DISCUSSION

Serum Cystatin C is a recognized indicator of renal disorders and an emerging biomarker for cardiovascular diseases (CVD) and impaired renal function [25]. This study delved into the variations in serum Cystatin C levels concerning gender, age, and BMI in a cohort of 180 healthy volunteers. Recently, new studies showed its role in predicting new-onset or deteriorating CVD[26]. Additionally, it has been suggested to play a part in amyloid-related brain illnesses, including Alzheimer's disease[27,28]. In humans, Cystatin C is produced as a chain of 120 amino acids by every cell with a nucleus (the DNA-containing center of the cell)[29]. It is synthesized in almost all tissues and body fluids. It is one of the most significant extracellular inhibitors of cysteine proteases as well as a robust inhibitor of lysosomal-proteinases, which are enzymes produced by a specific cell component that breaks down proteins. (It inhibits a certain class of protein-degrading enzymes from breaking down proteins outside of the cell)[30,31].

Previous studies offered contradictory findings regarding whether Cystatin C levels differ depending on gender. In adulthood, males have higher levels of Cystatin C than females, according to some researchers[32,33], whereas others did not find any statistically significant variations between them[34]. Some researchers even suggested that the statistically significant difference between Cystatin C concentrations in men and women was too minor to support a common reference range. Biological and hormonal differences between genders may contribute to variances in Cystatin C levels. According to research, hormonal variations, notably the effect of sex hormones, may have a role in the regulation of Cystatin C production and secretion Males may have higher amounts of Cystatin C due to hormonal impacts on its production [14].

In addition, Age-related variations in Cystatin C levels between genders were noted, particularly in older age groups. While males exhibited upper Cystatin C concentrations, statistical analysis indicated a minor difference. This prompts further exploration into the interaction between gender, aging, and renal function, considering that hormonal dynamics may evolve with age. In agreement with previous studies, results of this study, as shown in Figure (2), induced non-significant differences in Cystatin C concentration in healthy people above 40 years old, although higher Cystatin C concentrations were found in men, but not significant enough, according to statistical analysis, which was used to analyze data with p value ≤ 0.05.

Studies that have demonstrated typical age-related decreases in function in other physiologic domains are consistent with the idea that some kidney function declines represent normal aging[35]. Even in senior people who are healthy, there is a reduction in cardiac-output, maximum oxygen consumption, muscle strength, immunological function, metabolic rate, and various hormone levels with age[36]. Numerous studies have revealed that the concentration of Cystatin C is dependent on the healthy state and age of the kidneys[37–39]. Even after accounting for chronic medical conditions, a published study on Cystatin C concentrations in the USA found a significant and independent relationship between age and Cystatin C concentrations in people over 60 years of age[40].

According to this result and the study in Figure (3), there are significant differences in Cystatin C concentrations according to age. The results show a gradual increase in Cystatin C every 10 years between group studies of healthy volunteers, and these results are in agreement with many studies that provided results showing an increase in Cystatin C concentration proportionately with an increase in age, and normal-aging is usually accompanied by a decline in various physiological functions, commonly referred to as senescence. Studies have consistently demonstrated age-related decreases in different domains, such as cardiac output, maximum oxygen consumption, and muscle strength [41].

The kidneys are no exception to this phenomenon, and age-related changes in kidney structure and function can affect the filtration and clearance of substances like Cystatin C Thoughtful the age-related variations in Cystatin C levels is crucial for its clinical interpretation. Age-specific reference ranges may need to be considered when using Cystatin C as a biomarker for renal function or cardiovascular risk assessment. Clinicians should be mindful of these age-related trends when evaluating Cystatin C results in different patient populations. Additionally, recent researches have demonstrated a link between higher BMI and earlier phases of the renal disease continuum, including chronic kidney disease (CKD). Nonetheless, the correlation between high Cystatin C levels and BMI has not

been thoroughly investigated previously[42].

This study also examined Cystatin C concentration and its associations with weight and BMI. Numerous biologic pathways, including hormonal variables, inflammation, oxidative stress, and endothelial dysfunction, may be involved in the link between obesity and kidney disease[43]. Higher BMI levels indicate excess adiposity, which may be linked to the sympathetic nervous system and renin-angiotensin system activation, lipid deposition, hyperfiltration, and increased sodium absorption in the kidneys[44,45].

This feedback loop causes obesity-related declines in kidney function to develop into hypertension, which then causes additional kidney damage. The results of this study in Figure (4) showed significantly elevated levels in Cystatin C concentration with increase in weight, especially in people who were extremely obese. Excess excretory load, renal salt retention, hyperinsulinemia, insulin resistance, or renal lipotoxicity are a few of the ways that obesity can contribute to renal impairment. Increase in Cystatin C concentration in obese adults can be an early indicator of glomerulopathy and CKD. Obesity has been linked to a type of focal segmental glomerulosclerosis called obesity-related glomerulopathy, which could enhance the development of glomerulosclerosis[46].

CONCLUSION

In conclusion of this study reveals gender-based differences in level of Cystatin C, with higher in males. Age-related differences show a gradual elevated every decade, emphasizing the need for age-specific reference ranges. Additionally, Cystatin C levels correlate significantly with BMI, particularly in extremely obese individuals. The findings underscore the importance of considering demographic factors for accurate clinical interpretation and highlight Cystatin C's potential as an early indicator of renal impairment in the context of obesity.

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