Original Article

Renal Function Status in Postmenopausal Bangladeshi Women in a Tertiary Care Hospital

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Abstract

The study was done to find out the causes that of changes in renal function status in postmenopausal women. In Bangladesh there is no exact data on incidence of increased serum creatinine level and decreased creatinine clearance rate in menopausal women. This was descriptive type of cross sectional study carried out over a period of one year from July 2014 to June 2015 in the department of physiology, Mymensingh Medical College, Mymensingh. Women of reproductive age (25-45 years) and clinically diagnosed 100 menopausal women (45-70 years) were included in this study. A Convenience type of sampling technique was used for selecting the study subjects. Measurement of serum creatinine level and creatinine clearance rate was done as per the procedure. Data were expressed as mean±SD and statistical significance of difference among the groups were calculated by unpaired student's 't' test. The mean±SD of serum creatinine level and creatinine clearance rate in menopausal women were significant at 1% level of probability than women of reproductive age. This study revealed that postmenopausal women showed higher levels of serum creatinine & decreased creatinine clearance rate.

Key words: *Postmenopausal women, Serum creatinine, Creatinine clearance rate.*

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Introduction

Menopause occurs as a part of a women's normal aging process which is a natural life change, not usually a disease state or a disorder[1]. Menopause means permanent cessation of menstruation at the end of reproductive life due to loss of ovarian follicular activity. It is the point of time when last and final menstruation occurs. The clinical diagnosis is confirmed following stoppage of menstruation for twelve consecutive months without any other pathology[2]. Menopause is the stage in life when women gradually lose cyclical ovarian activity between the ages of 47 and 52 years. In many ways it is a reversal of the changes occurring at puberty. Menstruation rarely ceases abruptly but tends to become irregular and less frequent over a year or a little longer[3]. Although life expectancy has progressively increased, the average age of menopause has remained remarkably constant over the centuries. In present day management of menopause the ages of 45 and 55 years are probably best regarded as the limits of normality and women who have a menopause before age 45 years probably merit hormone replacement and those menstruating after 55 years merit investigation to exclude organic disease[4]. The leading theory regarding onset of menopause is primarily triggered by ovarian aging is supported by the coincident occurrence of follicular depletion, elevation of gonadotropins and menstrual irregularity with ultimate cessation[5]. There is decreased secretion of sex hormones and increased secretion of gonadotropins from pituitary[6]. The primary basis for progressive decrease and final cessation of cyclical function of reproductive organs at menopause lie in the ovary itself. The primordial follicles responsiveness to gonadotrophin gradually disappears and remaining few follicles becomes unresponsiveness to gonadotropin stimulation[7].The secretion of both FSH and LH are increased due to absent negative feedback effect of estradiol and inhibin or due to enhanced responsiveness of pituitary to GnRH. Rise in FSH is about 10-20 fold, whereas that of LH is about 3 fold[2]. Plasma progesterone and 17-hydroxy progesterone are reduced. Whatever amount of progesterone is present is contributed by adrenal gland. Prolactin level falls after menopause due to decrease in plasma estrogens[7].

Structural and functional changes resulting from age, and systemic diseases affecting the kidney, often cause a significant decrease in renal function[8].Serum creatinine was measured because it is most specific of 3 measures of kidney function (serum creatinine, urinary creatinine clearance, and blood urea nitrogen) available in NHANES III (third National Health and Nutrition Examination Survey)[9].Serum creatinine concentration affected by factors other than creatinine filtration, including sex age, race, diet, muscle mass, and the analytical method[10].Women appear more modest course of renal disease progression than men. The reason may stem from diet, difference in kidney structure, glomerular hemodynamic responses to stress, and the direct cellular effects of sex hormones[11].Serum creatinine reflects GFR more reliably than urea, as it produced from muscle at a constant rate and almost completely filtered at the glomerulus[12].Any rise in serum creatinine is sensitive indicator of kidney mal-function, because creatinine normally is rapidly removed from the blood and excreted[13]. The prevalence of severe renal impairment was greater for women than men (24% vs. 11 %) [14]. As muscle mass fall with age, less creatinine is produced each day. Renal tubular function declines with age, leading to loss of urinary concentrating ability[12]. In postmenopausal women with coronary artery disease (CAD), mild to moderate renal insufficiency (serum creatinine≥1.2 mg/dl) is associated with increased risk for cardiovascular events[15].

Serum creatinine and calculated creatinine clearance are the most convenient estimates of glomerular filtration rate (GFR)[16]. We used serum creatinine and estimated creatinine clearance to classify renal function[15].Creatinine clearance has been generally

accepted as a clinically useful measure of GFR despite some limitations[17]. Measurement of creatinine clearance, gives an estimate of the GFR, helps in early detection of renal failure[18].The GFR varies according to renal mass and correspondingly to body mass. It is conventionally corrected for body surface area (which equates with renal mass), which in normal human is approximately 1.73 m^2.[16]Tierney, McPhee and Papadakis found that the creatinine clearance is approximately 100 ml/min in healthy young women and 120 ml/min in healthy young men. It declines by an average of 0.8 ml/min/year after age 40 years as part of aging process, when normalized for body surface area of 1.73 m^2 .[19]The normal corrected GFR is 80- 120 ml/min/1.73 m^2, impaired renal function is 30- 80 ml/min/1.73 m^2 and renal failure is less than 30 ml/min/1.73 m^2 . The corrected GFR is approximately 8% lower in women and declines with age at an annual rate of 1 ml/min/1.73m^2 from the age of 40[16].

As serum creatinine is relatively inaccurate for estimating renal function, prediction formulae are commonly used for more precise renal function estimation[8]. Rapid estimation of GFR by using creatinine based mathematical equations, rely on the inverse relation of serum creatinine with GFR, along with adjustment factors measurable determinants of serum creatinine concentration (e.g., age, sex, body size, race)[20]. Renal function was estimated by the Cockcroft-Gault formula using serum creatinine determination[14]. It is most commonly used formula because of its ease of use and inclusion of age and weight as predictors of urinary creatinine excretion[17].Elevated levels of creatinine and drop in creatinine clearance rate reflected impaired renal function[21]. In clinical practice, clearance rate of endogenous creatinine, creatinine clearance rate (CCR), is the usual means of estimating GFR[22].The relationship between serum creatinine and glomerular function (GFR) is logarithmic[23]. In 2001, the National Kidney Foundation (NKF) issued a consensus statement recommending chronic kidney disease (CKD) as the preferred level and glomerular filtration rate (GFR) as the diagnostic test of choice[24]. Renal function biomarkers such as eGFR from serum creatinine are dependent on age and muscle mass[25].The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease (CKD) as either kidney damage or a decreased kidney glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for three or more months[26].

The reduction of e-GFR associated with increased risk of death and cardiovascular (CV) events, independently of traditional CV risk factors, menopausal duration and presence of metabolic syndrome[27]. The prevalence of anaemia increases as kidney function declines. As glomerular filtration rate increase, the risk to be anaemic will decrease dramatically[28]. The association between kidney function and cardiovascular disease is complex. In the Framingham Heart Study, body mass index, smoking and diabetes are predictors of impaired renal function[29]. Abnormal phosphate retention and subsequent elevation in parathyroid hormone (PTH) may occur from the early stage of renal impairment and negatively affects bone mineral density (BMD) [30]. Hypertensive kidney disease is less common in women compared to men; however this gender protective effect diminishes and tends to disappear with the onset of menopause[31]. Declining renal function is associated with subclinical atherosclerosis (vascular stiffness, brachial artery endothelial dysfunction, carotid artery intima-media thickening)[15].

After menopause incidence of chronic renal disease in women increases suggesting that loss of sex hormones contributes to the development and progression of kidney disease[31]. Nearly one billion and 240 million people worldwide have high blood pressure and diabetes respectively that number is expected to increase to 1.56 billion and 380 million by 2025. Of those with diabetes, about 40% will develop chronic kidney disease (CKD), which means that their risk of cardiovascular complications also increase[32].

Methods

This descriptive type of cross sectional study was carried out in the department of physiology, MMC, Mymensingh from July 2014 to June 2015. This period included the time for selection of study places, seeking permission from the appropriate authority, physical examination for both postmenopausal women (study group) and women of reproductive age (control group), editing, compilation, tabulation, analysis of data and report writing. The subjects were obtained from the department of gynecology and obstetrics, Mymensingh Medical College and Hospital, and locality of Mymensingh by convenience type of sampling technique. Total number of 200 subjects participated in this study. They were grouped as Group I (control group) consisting of 100 women of reproductive age; Group II (study group) consisting of 100 postmenopausal women. Age less than 25 years and more than 70 years; women who undergo hysterectomy or receiving hormone replacement therapy; diagnosed case of thyroid disorders, Cushing's syndrome, polycystic ovary, steroid and antipsychotic drug users were excluded. After selection the subjects were requested to attend the physiology department of Mymensingh Medical College at 8.00 am on a particular day. During visit, about 3ml of venous blood was collected from anticubital venepuncture by a disposable syringe with a gentle pull and the blood was taken in a dry and clean test tube, labeled with name of subject, with date and time of blood collection. During transfer of blood to avoid haemolysis, at first the needle was removed from the syringe and touching the nozzle to the side of test tube the blood was pushed with minimum force. The blood samples were carried to the laboratory within 2 hours of collection of samples. The blood sample (2ml) in test tubes was centrifuged at 3000 rpm for 5 minutes.

After centrifugation the supernatant serum was collected and experiment was carried out immediately after sampling. In case of any delay samples were stored in a refrigerator at 4°C for up to 24 hours. Serum creatinine was measured by Enzymatic Colorimetric method, Creatinine clearance rate was calculated by using Cockcroft-Gault equation.

After collection of data, the editing, coding, verification were done manually. Master sheets were prepared first for the purpose of tabulation. The results were calculated and analyzed by using SPSS (statistical package for social science, version 11.5), scientific electronic calculator and simultaneously with a computer assisted program like Microsoft excel. Unpaired student's 't' test was applied to find the effects of decrease in female sex hormone on blood pressure. The value of p was <0.0001 to indicate highly significant and p<0.005 to indicate simply significant or statistically significant.

Results

The study included serum creatinine expressed in mg/dl (conventional units) and creatinine clearance rate expressed in ml/min. Data were expressed as mean±SD. Average age of reproductive aged women (control group) and postmenopausal women (study group) were 32.89±5.25 and 54.62±4.68 respectively which was highly significant at 1% level of probability (p<0.0001). The mean±SD of serum creatinine of study group (1.02±0.15) was higher than control group (0.85±0.16) and highly significant at 1% level of probability (p<0.0001). Mean difference was 0.17and 95% confidence interval was 0.12to 0.21. It means that if we take same sample 100 times in 95% cases the MD (mean difference) will lies between the lower limit 0.12and upper limit 0.21(Table I and Figure 1).The mean±SD of creatinine clearance rate of study group (62.11±14.19) was lower than control group (82.40±18.30) and highly significant at 1% level of probability (p<0.0001). Mean difference was 20.29and 95% confidence interval was 15.72to 24.86. It means that if we take same sample 100 times in 95% cases the MD (mean difference) will lies between the lower limit 15.72and upper limit 24.86(Table I and Figure 2).

Table I: Shows different parameters for comparative study between study and control group

Parameters	Study group Mean±SD	Control group Mean±SD	Mean Difference (MD)	't' value	P value	95% confidence interval of MD	
						Lower limit	Upper limit
Age	54.62±4.68	32.89±5.25	21.73	30.86**	0.0001	20.34	23.11
Serum creatinine	1.02±0.15	0.85±0.16	0.17	7.57**	0.0001	0.12	0.21
CCR	62.11±14.19	82.40±18.30	20.29	8.76**	0.0001	15.72	24.86

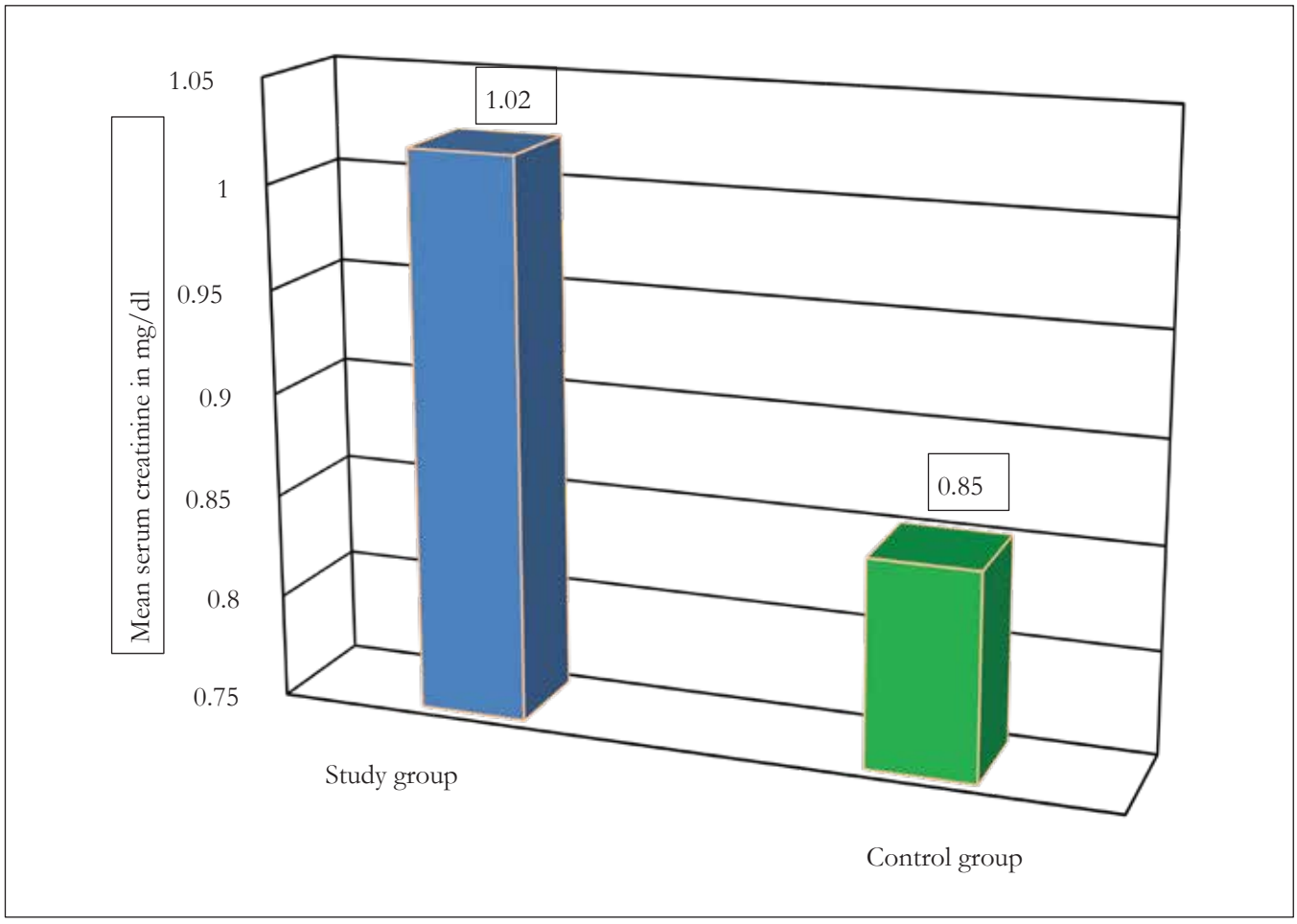

Figure 1: Bar diagram shopwed of mean serum creatinine (mg/dl) in study and control group

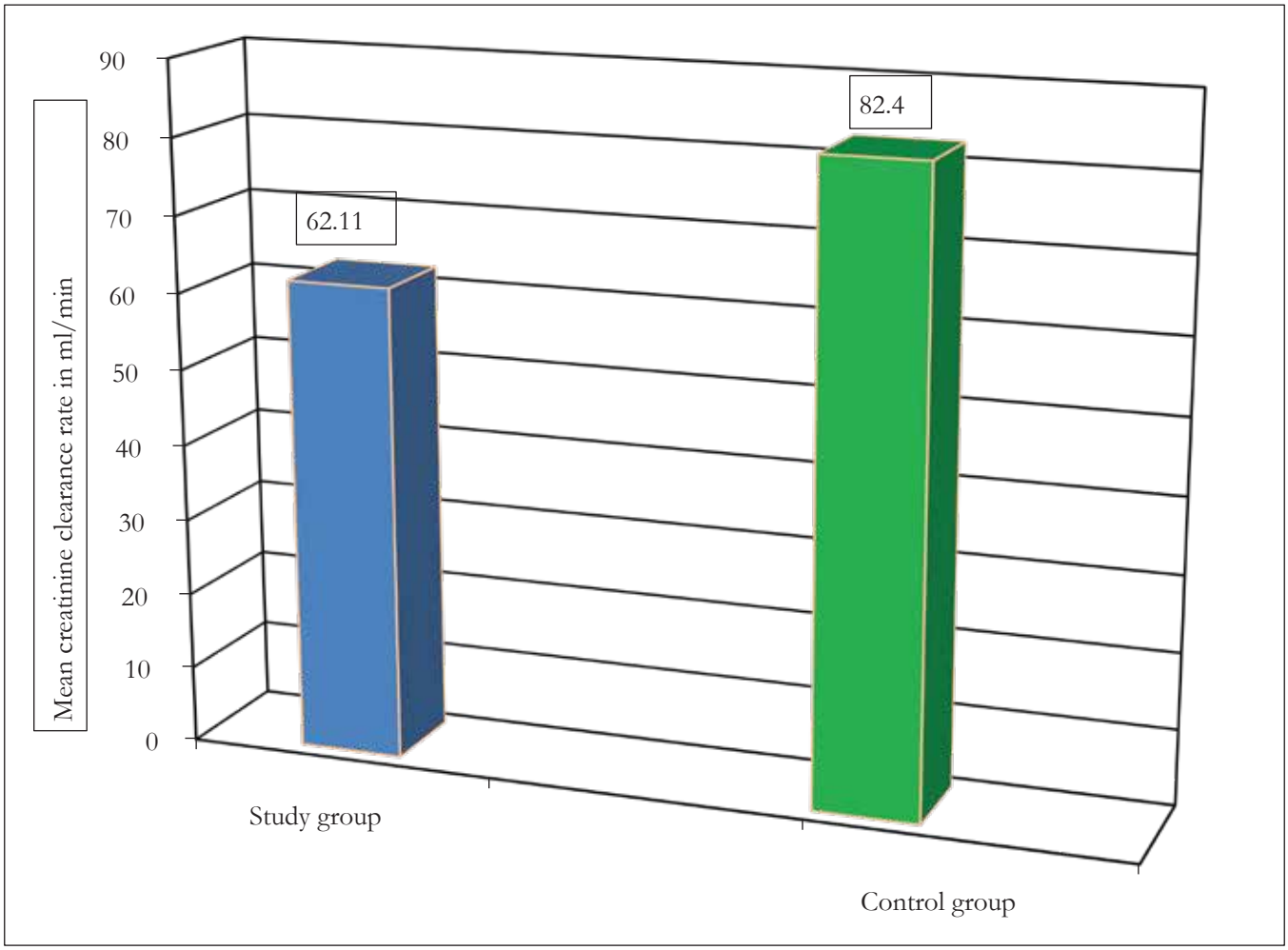

Figure 2: Bar diagram showed of mean creatinine clearance rate (ml/min) in study and control group

Discussion

Serum creatinine

In this study serum creatinine of (control group) women of reproductive age (group I) and (study group) postmenopausal women (group II) were 0.85±0.16 mg/dl and 1.02±0.15 mg/dl respectively. This result was significantly increased at 1% level of provability ($p<0.0001$).

The result is consistent with that of Ghasemi et al., this study proposed that serum creatinine levels were higher in menopausal women, aged over 50 years[10]. According to Negri, Lombas and Zanchetta a recent study on data from the NHANES III (Third National Health and Nutrition Examination Survey 1988-1994) found that prevalence of severe renal impairment was greater for women than men (24% vs. 11%)[14]. This was examined in Yamashita et al. (2003, p. 601) that decreased renal function was mainly influenced by age, not by sex or menopause.

Earlier research demonstrated that women were categorized as having normal renal function (creatinine<1.2 mg/dl), mild renal insufficiency (1.2-1.4 mg/dl) and moderate renal insufficiency (>1.4 mg/dl)[33]. A recent study found that women with mild renal insufficiency were older, had higher systolic blood pressure and greater prevalence of hypertension, diabetes and menopause[15].

After menopause, the incidence of renal disease increases suggesting that the loss of sex hormones contributes to the development and progression of kidney disease[31]. A more recent study has shown that estrogen helped to protect against kidney disease and may exert certain cellular effects on the kidney because it can suppress the growth of scar tissue as well as affect various growth factors which impact the kidney[34]. It has been claimed that gender affects the incidence, prevalence, and progression of many renal diseases. Female sex hormones, such as estradiol, may slow the progression of renal disease[11].This data are important because Herrera et al. have found that the risk of development of hypertensive kidney disease is less common in women compared to men, however this gender protective effect diminishes and tends to disappear with the onset of menopause[31].

Creatinine clearance rate

In this study creatinine clearance rate of (control group) women of reproductive age (group I) and (study group) postmenopausal women (group II) were 82.40±18.30 ml/min and 62.11±14.19 ml/min respectively. This result was significantly decreased at 1% level of provability ($p<0.0001$).

According to Nordin et al. creatinine clearance rate were lower in postmenopausal women than premenopausal women after correction for surface area and age[35].A recent study suggest that whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in glomerular filtration rate (GFR)[26].It has been argued that in clinical practice, the clearance rate of endogenous creatinine, the creatinine clearance rate (CCR), is the usual means of estimating GFR[22]. Renal function biomarkers such as eGFR from serum creatinine are dependent on age and muscle mass[25]. Silbiger and Neugarten in their recent research paper found that women appear to have more modest course of renal disease progression than men. The reason for this finding may stem from diet, difference in kidney structure, glomerular hemodynamic responses to stress, and the direct cellular effects of sex hormones[11]. Menopause is accompanied by increased risk of chronic disease. Elevated levels of creatinine and drop in estimated glomerular filtration rate reflected impaired renal function[21]. It has been argued that renal function should be assessed by creatinine clearance rate rather than serum creatinine in elderly because renal impairment can be masked by an apparently normal serum creatinine level[30]. This data are important because the prevalence of traditional risk factors for cardiovascular disease is increased in patients with impaired kidney function and these risk factors predict the start of chronic kidney disease[29].

Conclusion

From the research studies it is evident that hormonal and metabolic factors in postmenopausal women due to decline of female sex hormones cause alteration of serum creatinine and creatinine clearance rate.

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