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Association of Uric Acid, Urea and Creatinine with Body Mass Index, Age and Gender.

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ABSTRACT

Obesity is one of main metabolic diseases causes worldwide. This metabolic disorder contributes greatly to the significant proportion of the burden of renal damage and dysfunction. The aim of this study is to assess the effect of body mass index (BMI) in males and females of different age on kidneys functions indicated by serum uric acid, urea and creatinine concentrations. Serum uric acid, urea and creatinine was measured in a total of 240 healthy individuals (120 males and 120 females) aged 18-60 years. Analysis of variance (ANOVA) was used to evaluate the effect of age, sex and body mass index (BMI) on serum uric acid, urea and creatinine concentrations.A positive correlation was detected between BMI and serum uric acid in both males and females of different ages. Serum creatinine and urea levels were found to have a significant positive correlation with BMI only at age ≥45 years in both males ($p=0.0098$, $p=0.0489$) and females ($p=0.0149$, $p=0.0487$) respectively. When the interaction between sex and BMI was considered, statistically significant difference in serum uric acid levels was demonstrated in all age groups ($p<0.0001$). However, serum creatinine and urea levels showed no significant differences up to age of 45 years. At and above age of 45 years, statistically significant difference in both serum creatinine and urea levels ($p<0.0056$ and $p<0.0054$ respectively) were found. The morbidly obese males in all age groups showed uric acid levels that let them be diagnosed to have hyperuricemia (based on the reference ranges given by Fortress diagnostic limited 2011: males' uric acid cut off 416.5 µmol/L and females 339 µmol/L). Whereas, only the morbidly obese females at age ≥45 years have uric acid level that indicates hyperuricemia. The morbidly obese females <20 years or 20-44 years seem to be at the border line of hyperuricemia. Our study indicates that there is a positive relationship between BMI and

serum uric acid among healthy subjects. Obesity may potentially serve as a novel clinical indicator for identifying patients with hyperuricemia. We demonstrated a sex difference in the incidence of hyperuricemia which may reflect a sex difference in renal uric acid clearance. Our study also showed that serum creatinine level is significantly directly correlated with BMI at age of 45 years or above. BMI is an independent predictor of creatinine increase in adult aged 45 years or more. The prevention of obesity and weight control are exceptionally important in the protection of renal function

Introduction

Obesity is linked to several functional and structural alterations in the kidney. Renal diseases mainly proceed from hemodynamic abnormalities, obesity related dysfunction, metabolic abnormalities, and mast cell related kidney inflammation mechanisms (Roa and Zhang, 2006).

Body mass index (BMI) is one of the predictors of chronic kidney disease (Ishizaka et al., 2009). Obesity contributes to the deterioration of renal function in patients with under-lying renal disease (Praga et al., 2000; Praga et al., 2001; Elsayed et al., 2008; Tsujimoto et al., 2014).

Obesity can directly cause kidney diseases, as the kidneys have to work harder, filtering above the normal level, known as hyper-filtration, to meet the metabolic demands of the increased body mass index (BMI) in obese individuals particularly those with high blood pressure and diabetes (Kambham et al., 2001).

As indirect cause obesity increases the risk of the major chronic kidney disease, risk factors- type 2 diabetes and high blood pressure. A study done by Kambham et al., showed a dramatic increase of histological proven renal diseases in obese patient in the absence of diabetes (Kambham et al., 2001).

The patients had rapidly progressive renal disease. Furthermore, Obesity is an important risk factor for progression of renal disease in IgA nephropathy (Bonnet et al., 2001) and is also associated with an enhanced risk of chronic graft dysfunction after renal transplantation (Meier-Krische et al., 2002).

A study in mice, by Carmo et al., in 2009 revealed that kidney dysfunction owing to obesity may have a significant positive correlation with increases in blood pressure (Carmo et al., 2009). However, Pinto-Sietsma et al. in 2003 revealed that the relationship between body mass index (BMI) and end-stage renal disease persists even when adjusted for diabetes and hypertension (Pinto-Sietsma et al., 2003).

The animal experiments of Henegar at al. (2001) showed that obesity-induced glomerular damage can be particularly rapid. The organizational, biochemical, and renal functions of dogs fed high-fat meals changed after just 7-9 weeks (Henegar et al., 2001).

The present study was aimed to contribute to the current literature on biochemical area of obesity, by focusing on the effect of age, gender and body mass index (BMI) on kidneys functions indicated by uric acid levels, urea levels and creatinine levels in the blood.

Materials and Methods

A prospective, non-randomized study was performed in a total of 240 healthy individuals (120 males and 120 females) aged 18-60 years. The subjects were divided into 4 groups according to their body mass index (BMI) (group1 with BMI <25 kg/m², group 2 with BMI 25-29.9 kg/m², group 3 with BMI 30-39.9 kg/m² and group 4 with BMI ≥40 kg/m². Each group contained a total of 60 indivduals (30 males and 30

females) and subdivided into 3 sub-groups: *A* (Age <20 years), *B* (Age 20-44 years), *C (*Age ≥45 years) each subgroup contains (10 males and 10 females). The body mass index (BMI) was calculated as weight/ height² (kg/m²). Overweight and overall obesity were defined according to the World Health Organization (WHO) criteria (WHO, 2000), which defined the obesity as BMI ≥ 30.00 and placed a desirable (normal) range of body mass index (BMI) to be at 18.5-24.9 kg/m², overweight/pre-obese (25-29.9 kg/m²), obesity (class 1 and 2) (30-39.9 kg/m²) and class 3 obesity-morbidly obese (≥ 40 kg/m²). This study included overweight and obese subjects as per by WHO criteria (2000), from both the genders in age range of 18 to 60 years and restricted to persons older than 18 to reduce possible confounding by growth and development. Individuals with a known history of Kidneys diseases were excluded from this study.

After being thoroughly informed of the purpose, requirement, and procedures of the study informed written consent was obtained from all participants. All participants completed a questionnaire, including age, sex, family or personnel disease histories, specially kidneys diseases.

All laboratory measurements were performed on fasting venous blood samples which were collected from each individual after 12 hours fasting as per the standard guidelines and protocol (Simundic et al., 2014), under strict aseptic precautions, and were allowed to clot 30 minutes at room temperature; serum was separated by centrifugation at 3000 rpm for 4-5 minutes for biochemical analysis (Simundic et al., 2014).

All the samples were processed within 1 hour from the time of collection. The serum uric acid levels were measured by Uricase–PAP method (Trinder, 1969 and Trivedi et al., 1978), serum creatinine levels were measured by kinetic Jaffe method (Miller et al., 2005) and urea levels assay were conducted by Urase-GLDH (Traynor et al., 2006) using Cobas 6000 analyzer, Roche (Vesna et al., 2011).

Statistical analysis

All statistical analyses were carried out using (SAS 2008) where *P*-values of less than ($P \leq 0.05$) was considered statistically significant. Data obtained were evaluated by Analysis of variance (ANOVA) and were subjected to statistical analysis using the general linear model procedures of SAS software (SAS, 2008). The statistical differences between means were analyzed by Duncan's multiple range tests ($P \leq 0.05$). All values expressed as the statistical means a ± standard error of the mean (SEM) (SAS, 2008).

Results

Serum uric acid, urea and creatinine levels in males, grouped by age and BMI are shown in Table (1), Serum uric acid, urea and creatinine levels in females grouped by age and BMI are shown in Table (2) and the effect of two-way interaction (sex*BMI) on serum uric acid, urea and creatinine levels are shown in Table (3).

Table (1): Serum uric acid, urea & creatinine levels in males grouped by age and BMI.

	Age	BMI					
		A	**B**	**C**	**D**	**SEM**	***P-value***
Serum uric acid	<20	274.10^{c}	320.10^{bc}	369.70^{b}	440.80^{a}	21.895	<.0001
(µmol/L)	20-44	298.80^{c}	361.00^{b}	408.00^{ab}	425.50^{a}	17.771	<.0001
	≥45	327.80^{b}	332.10^{b}	401.60^{ab}	437.40^{a}	27.124	0.0160
Urea**(mmol/L)**	<20	3.540	3.760	3.870	4.200	0.280	0.4204
	20-44	3.960	3.990	4.020	4.080	0.2163	0.9822
	≥45	3.8600^{b}	4.6600^{ab}	4.8600^{a}	4.8600^{a}	0.2802	0.0489
Creatinine	<20	47.70^{b}	51.40^{ab}	54.60^{ab}	59.50^{b}	3.094	0.0659
(µmol/L)	20-44	73.70	74.30	74.90	78.00	3.0254	0.7537
	≥45	77.800	82.000	94.100	95.700	5.6619	0.0098

*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

Uric acid, urea and creatinine showed highest levels in group D (morbidly obese males) and lowest levels in group A (normal BMI) in all age categories. Males at age<20 and up to 44 years showed increase in urea and creatinine levels with the increase of BMI, but of no statistically significant difference. Whereas at age ≥45 years a statistically significant increase of urea and creatinine levels with the increase of BMI were reported *(P=0.0489 and P=0.0098 respectively)*. Uric acid levels in males of all age groups were found to have a statistically significant increase with the increase of BMI.

Uric acid is more affected in males of all age category specially in morbid obesity group (≥40 kg/m²).

Urea is affected ascendingly.

Table (2): Serum uric acid level s, urea levels & creatinine levels in females grouped by age and BMI.

	Age	BMI					
		A	**B**	**C**	**D**	**SEM**	***P-value***
Serum uric acid	<20	241.90^{c}	272.90^{bc}	300.00^{ab}	334.30^{a}	15.360	0.0012
(µmol/L)	20-44	206.10^{b}	266.70^{b}	304.00^{a}	327.70^{a}	18.745	<.0001
	≥45	225.70^{b}	233.70^{b}	329.30^{a}	352.20^{a}	21.816	0.0002
Urea**(mmol/L)**	<20	3.210	3.270	3.660	3.820	0.256	0.2734
	20-44	2.960	3.160	3.220	3.360	0.2664	0.7622
	≥45	3.8900	3.9900	4.1100	4.5400	0.3146	0.0487
Creatinine	<20	51.10	51.10	52.50	51.60	2.462	0.9746
(µmol/L)	20-44	52.50	56.70	57.90	58.10	2.6428	0.4159
	≥45	51.300^{b}	55.200^{b}	58.400^{a}	64.500^{ab}	2.7931	0.0149

*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

Group D have highest uric acid, urea and creatinine levels (morbidly obese females) and group A have lowest levels (normal BMI) in all age categories. Same as males, females were reported to have a weak non-significant increase in urea and creatinine levels with the increase of BMI from age<20 up to 44 years. At age ≥45 years urea and creatinine levels show a statistically significant increase with the increase of BMI *(P=0.0487 and P=0.0149 respectively)*.

Females of all age groups were found to have a statistically significant increase in uric acid levels

with the increase of BMI. Uric acid in females is more affected at age ≥45 years.
The data showed that males had higher uric acid, urea and creatinine levels than that of females, both males and females had a statistically significant increase in urea and creatinine levels with the increase of BMI only at age ≥45 years. Uric acid level is more affected in both sexes at age ≥45 years.

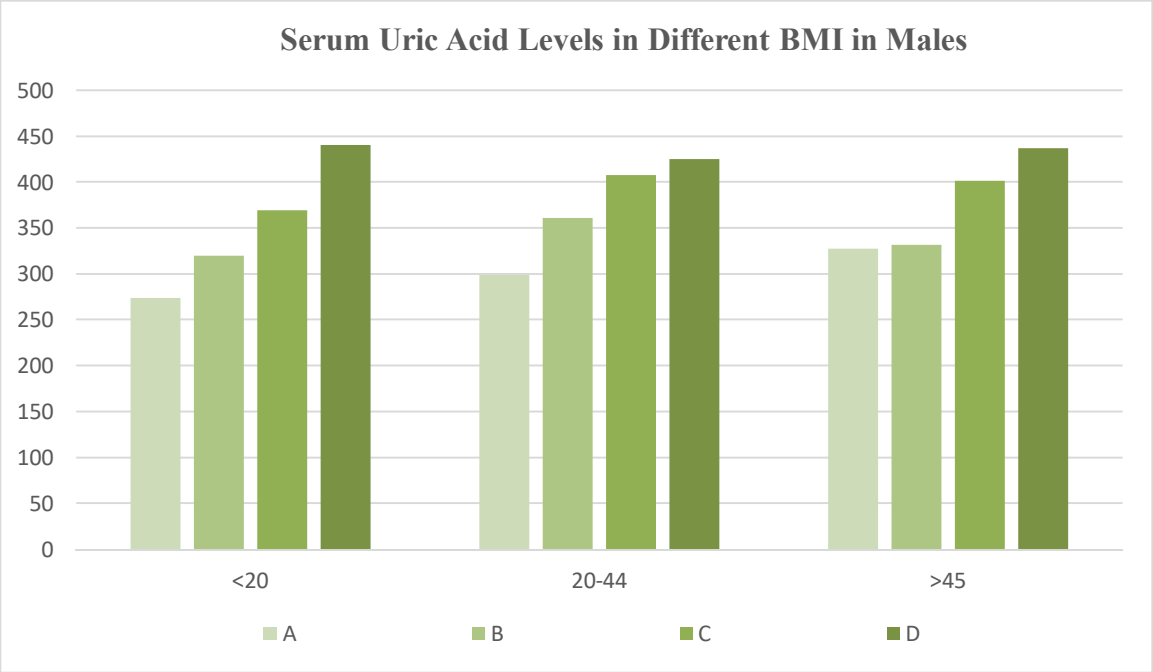
Table (3): Effect of two-way interaction (sex*BMI) on serum uric acid, urea and creatinine levels.

	Age	BMI					
		A	**B**	**C**	**D**	**SEM**	***P-value***
Serum uric acid	<20	258.00^{d}	296.50^{c}	334.85^{b}	387.55^{a}	13.373	<.0001
(µmol/L)	20-44	252.45^{c}	293.85^{b}	356.00^{a}	376.60^{a}	12.915	<.0001
	≥45	276.75^{b}	282.90^{b}	365.45^{a}	394.80^{a}	17.404	<.0001
Urea**(mmol/L)**	<20	3.405	3.705	3.765	3.790	0.190	0.4560
	20-44	3.460	3.575	3.650	3.690	0.1716	0.7913
	≥45	3.9250	4.3750	4.3850	4.7000	0.2106	0.0056
Creatinine	<20	49.40^{b}	51.25^{ab}	53.55^{ab}	55.55^{a}	1.977	0.1478
(µmol/L)	20-44	63.10	65.50	66.40	68.05	2.0085	0.3727
	≥45	66.500^{b}	66.650^{b}	79.300^{a}	77.050^{a}	3.1566	0.0054

*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

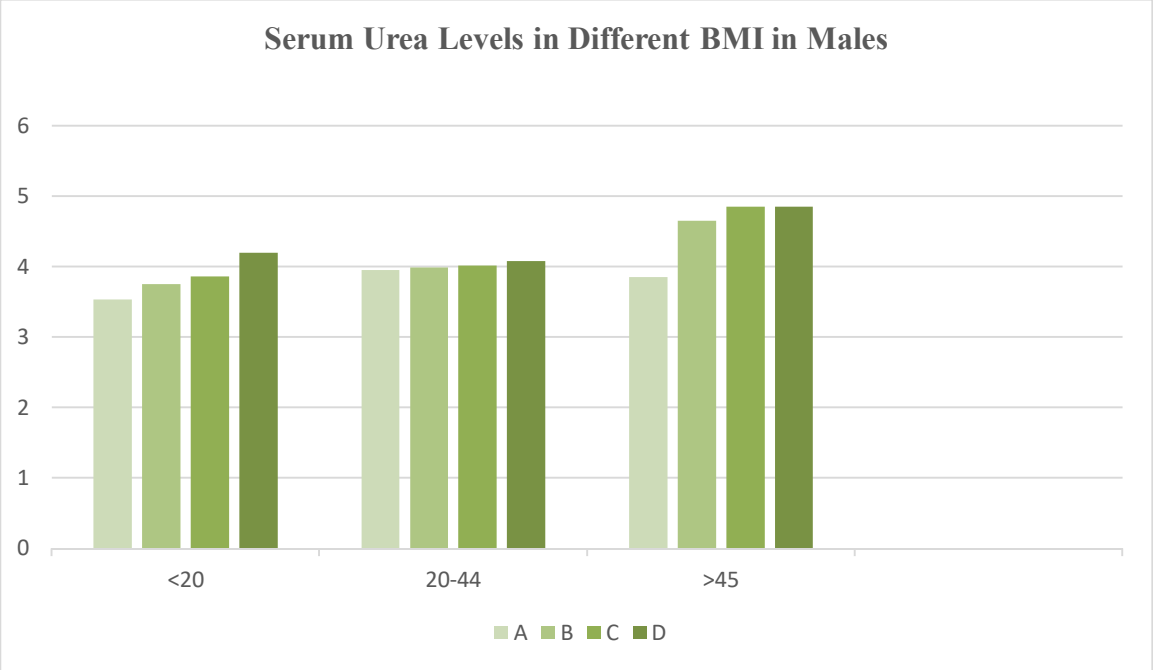
Uric acid, urea and creatinine showed highest levels in group D (morbidly obese) and lowest levels in group A (normal BMI). When we consider the interaction between sex and BMI a statistically significant difference in uric acid level *(P<0.0001)* was found in all ages, but not in urea and creatinine levels for up to 44 years old. Then at age of ≥45 a significant increase in urea *(P=0.0056)* and creatinine (*P=0.0054)* levels together uric acid level were reported. Creatinine is less affected in both sexes at age <20 and more affected at age >45 (ascending effect) whereas urea is less affected in both sexes at age <20-44 and more affected at age >45 (ascending effect).

Fig.1



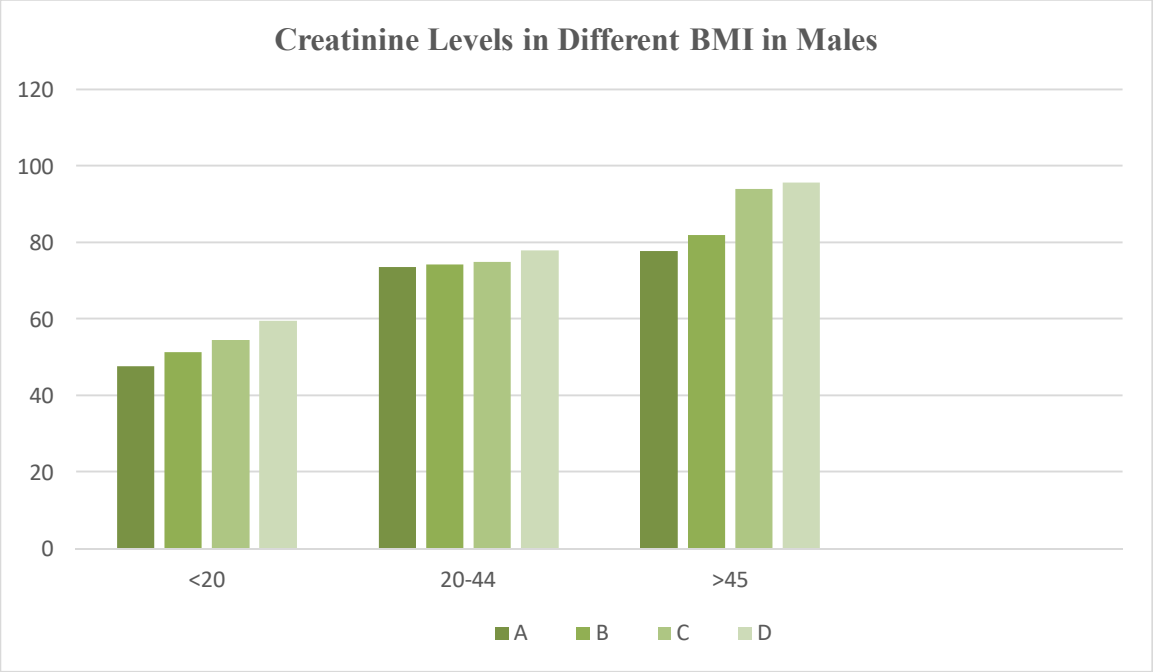
*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

Fig. 2



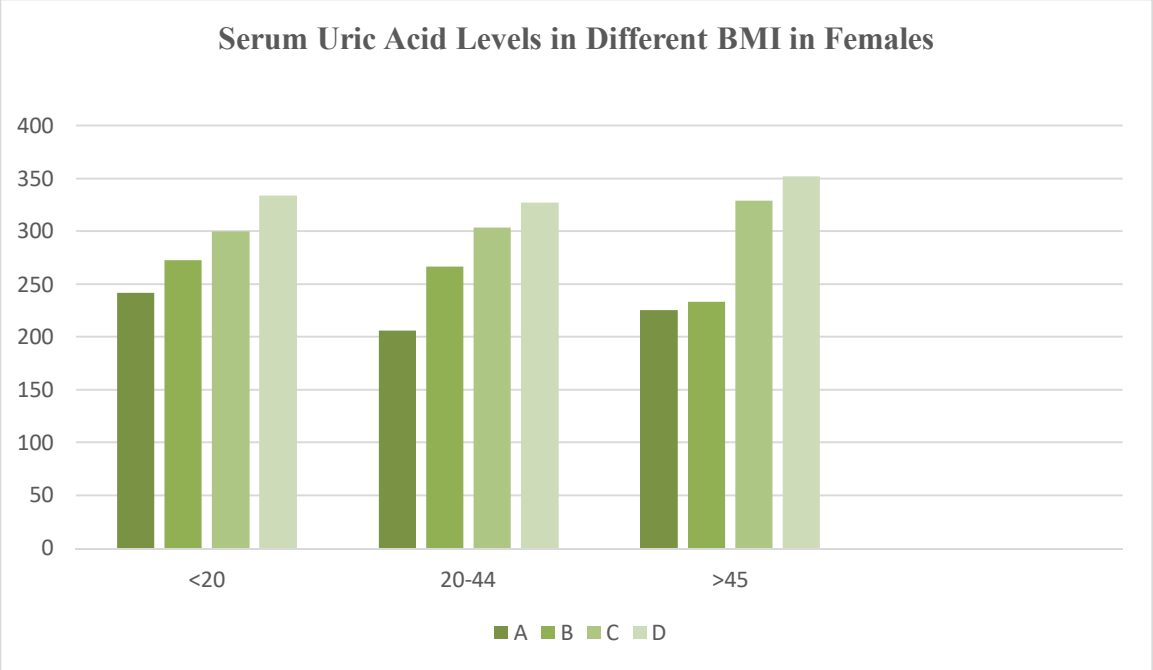
*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

Fig. 3



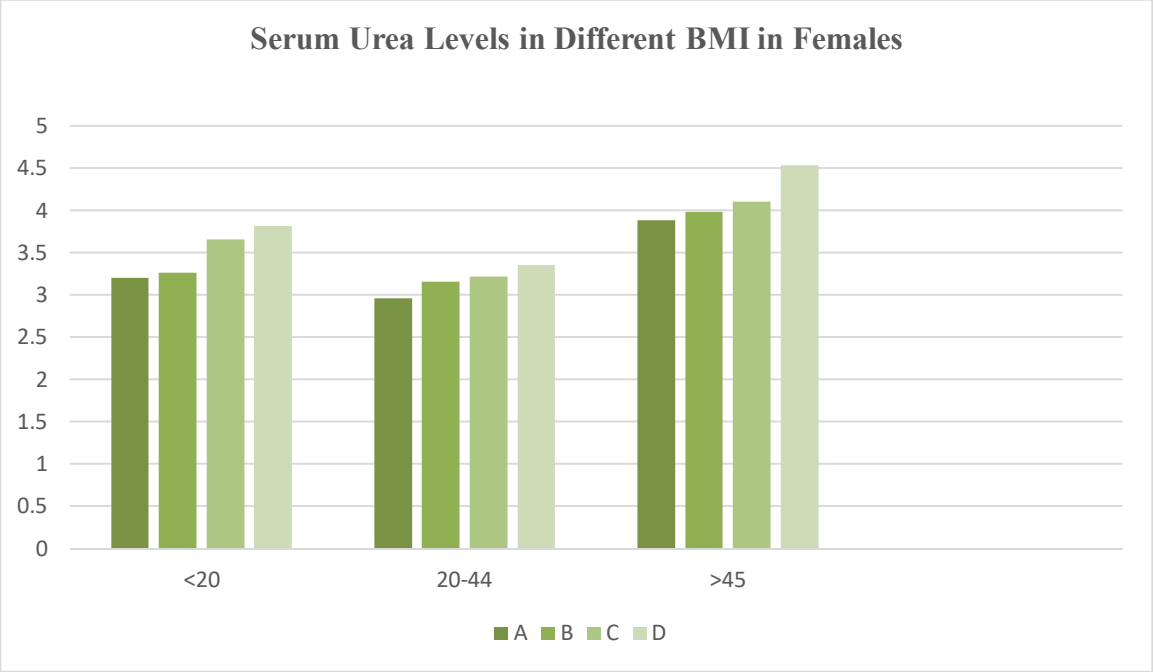
*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

Fig. 4



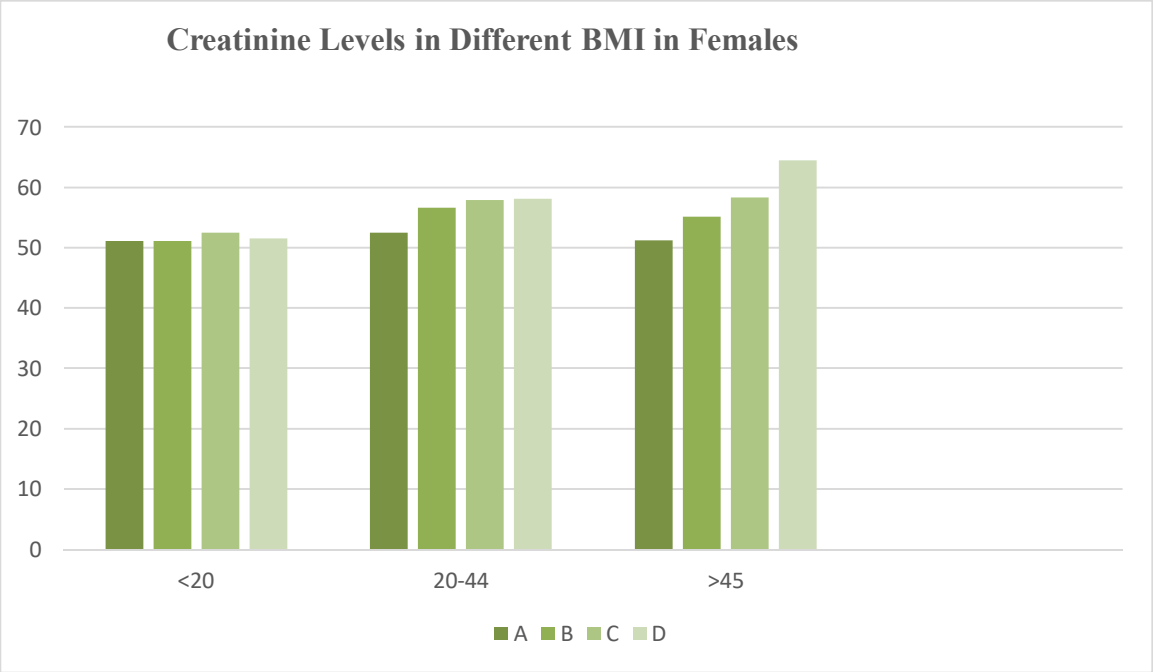
*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

Fig. 5



*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

Fig. 6



*(**A**: normal BMI <25 kg/m², **B**: overweight BMI 25-29.9 kg/m², **C**: obese BMI 30-39.9 kg/m², **D:** morbidly obese BMI ≥40 kg/m²).

There was a positive correlation between BMI and serum uric acid in both males (Fig. 1) and females (Fig. 2) at different ages. Whereas positive correlations between BMI and serum creatinine and urea levels were found in both males (*p =0.0098*, *p=0.0489)* (Fig. 3 and Fig. 4) and females *(p=0.0149, p=0.0487*) (Fig. 5 and Fig. 6) only at age ≥45 years respectively.

When we considered the interaction between sex and BMI, we found statistically significant difference in serum uric acid levels in all age groups *(p<0.0001),* while Serum creatinine and urea levels showed no differences up to 45 years, then they started to have statistically significant difference at this age and above.

The morbidly obese males in all age groups showed uric acid levels that let them be diagnosed to have hyperuricemia (based on the reference ranges given by Fortress diagnostic limited 2011: males' uric acid cut off 416.5 µmol/L and females 339 µmol/L). Whereas, only the morbidly obese females at age ≥45 years have uric acid that indicates hyperuricemia. The morbidly obese females <20 years or 20-44 years seem to be at the border line to have hyperuricemia.

Discussion

Data in the literature indicates that BMI is a strongly associated with prevalent hyperuricemia, which has important public health ramifications given that approximately about 500 million adults worldwide are obese and 1.5 billion are overweight (Finucane et al., 2011).

BMI is thought to be a more valuable prediction marker for the risk of elevated serum uric acid level. For the clinical doctors, BMI is more attractive for it is easy to get. Therefore, doctors are easier to predict the individuals' risk of hyperuricemia or gout.

Although several studies have previously demonstrated association between serum uric acid and body weight (Masuo et al., 2003, Charlotte et al., 2009), the relationship between BMI and the incidence of hyperuricemia and the difference between males and females was not well known. The present study was done in age matched overweight, obese and morbidly obese groups and controls to find out obesity adverse effect on renal functions from parameters (uric acid, creatinine, and urea levels).

This study has demonstrated that serum uric acid was positively correlated with BMI in healthy subjects. When subjects were divided into different groups according to BMI levels, the level of serum uric acid increased in higher BMI groups, especially in morbidly obese subjects. However, one of the main findings of the present study were that morbidly obese males in all age groups showed uric acid levels that let them be diagnosed to have hyperuricemia, whereas, only at ≥45 years the morbidly obese females have uric acid that indicates hyperuricemia.

Our study results are consistent with those of others. Studies conducted on the Japanese (Iseki, 2006; Iseki et al. 2004) and Malay populations (Shankar et al., 1910-1918) have demonstrated a male sex-specific association between BMI and kidney disease. Similarly, Chang et al., (2018) observed a higher male prevalence among overweight and obese chronic kidney disease patients. Oyama et al. in 2006 demonstrated a sex difference in the incidence of hyperuricemia among children 9-15 years old. Cosa et al, in 2002 also detected boys to have high uric acid levels than girls.

Our results are also in line with other studies that demonstrated, men to exhibit a higher risk of kidney disease and develop the disease earlier in life than women because of hormonal and lifestyle influences (Hopper et al., 1981; Gretz et

al., 1989; Tozawa et al., 2002; Neugarten et al., 2000).

An explanation may be BMI reflects visceral fat more efficiently in men than in women (Horber et al., 1997; Kuk et al., 2005), which may reflect sex difference in renal clearance.

The association between BMI and uric acid may be explained by that obese subjects have excessive fat accumulation in obesity which could produce and secrete uric acid and is relatively associated with overproduction-type hyperuricemia (Tsushima et al, 2013). This may provide a possible mechanism for the relationship between BMI and serum uric acid.

Russo LM et al, in 2009 explained that the increase in serum uric acid may be due to the decrease in renal blood flow, which stimulates urate reabsorption in obese and hypertensive individuals.

Another explanation may be that increased body mass index, raises blood pressure (Bartosh and Aronson, 1999; Dyer and Elliot, 1989) which in turn produces unfavorable effects and changes in kidney resulting in increased tubular secretions ending in increased blood urea, creatinine and uric acid levels. Increased blood pressure causes structural changes and metabolic demands by the kidney which first results in renal hyper-fusion and then in renal hyperfiltration. Basically, renal hyper-fusion state leads to glomerular re-absorption of blood urea, creatinine, uric acid. However, considering the strong association between hyperfiltration and risk of rise in these biochemical (Blood urea, creatinine, uric acid) parameters, it should be regarded as a precursor of loss of renal function in obese condition.

The result may be a vicious cycle of renal damage and nephron loss leading to more severe hypertension, glomerular hyperfiltration and further renal damage. Glomerular pathology progresses to glomerulosclerosis and eventually the renal tubules may also become ischemic and gradually atrophic.

Anvekar N.S. et al, in 2004 stated that an elevated blood urea nitrogen may represent an independent marker of renal dysfunction, which would further support a well-established association between renal disease and cardiovascular diseases.

Our analysis clearly indicated serum creatinine and urea levels to be significantly directly correlated with the BMI in both males and females at age ≥45 years. These findings matched by those of Uemura et al. (2011), who reported that serum creatinine concentrations differ significantly according to gender and age, also our findings are in the line with a cross sectional analysis from Turkey, which found ageing to strengthen the association between BMI and chronic kidneys disease (Suleymanlar et al., 2011).

One explanation could be that obesity is a chronic condition which could persist for decades in most affected individuals and older age is associated with a higher prevalence of comorbid conditions and a high short-term mortality, and it is therefore possible that age may modify the association of BMI with outcomes such as kidney disease.

Aging itself causes increased glomerular permeability, decreased individual glomerular volume, glomerular sclerosis, and decreased nephron numbers (McNamara et al., 2009). These effects could superimpose on the changes induced by obesity and result in a more marked effect on kidney functions in older individuals. The observation that in obesity older ages (≥45 years) were associated with higher values of creatinine and urea increasing the risk of progressive loss of kidney function in our study also supports this hypothesis.

Conclusion

Our study demonstrates a positive relationship between BMI and serum uric

acid among healthy subjects. Obesity may potentially serve as a novel clinical indicator for identifying patients with hyperuricemia. We demonstrated a sex difference in the incidence of hyperuricemia which may reflect a sex difference in renal uric acid clearance.

Our study also showed that serum creatinine level to be significantly directly correlated with BMI in both sexes at age of 45 years or above. BMI was an independent predictor of creatinine increase in adult aged 45 years or more. The prevention of obesity is exceptionally important in the protection of renal function.

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