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Serum uric acid as a diagnostic marker in metabolic syndrome children

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Abstract

Background:*Pathogenesis of metabolic syndrome is very complex. Several studies support the concept that oxidant/antioxidant imbalance may play an important role in its manifestations****.*** *Uric acid (UA) is a circulating marker for oxidative damage.The study aimed to investigate the potential association of UA and metabolic syndrome.****Methods:****From 129 random obese pediatric patients we enrolled 26 patients with metabolic syndrome randomly with percentage of 20.1% , and take matched control with same number. In Our Study we have evaluated 26 obese prepubertal children with metabolic syndrome. A control group of twenty six were taken. All children were subjected to full history taking, clinical examination including: anthropometric (waist circumference and body mass index) and blood pressure measurement, Lipid profile and serum uric acid levels were determined .****Results:****there was statistical significant increase in anthropometric measures, systolic blood pressure (SBP) and diastolic blood pressure (DBP), plasma glucose level (FPG),lipid profile (triglycerides, total cholesterol and low density lipoproteins (LDL) and Uric acid compared with control. In obese metabolic patients , there was positive correlation between body mass index, waist circumference, SBP, DBP,FBG, triglycerides, total cholesterol, LDL and serum UA, but significant negative correlation of serum UA and high density lipoprotein.UA at a level of 4.3 was the best cut- off value for metabolic patients with sensitivity 70% and specificity 96.3%, and this maximizing sensitivity and specificity to predict future metabolic syndrome and their area under the curve was 0.79.****Conclusion:*** *Serum uric acid is a good diagnostic marker in metabolic syndrome children*

Key words: *metabolic syndrome- Uric acid- Evaluation.*

I. Introduction:

In recent decades, the prevalence of overweight and obesity has become increasingly common such that it is now the major nutritional problem worldwide. Obesity occurs when dietary energy intake exceeds energy expenditure and has arisen in many societies due to an increasingly “obesogenic” environment in which physical activity has declined and yet children continue to be exposed to unhealthy, energy-dense diets. Additional risks for the development of obesity also include psychological issues and genetic factors **(1).**

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The prevalence of childhood obesity has increased 8-fold since 1975 and the combined prevalence of overweight and obesity may be as high as 23% worldwide[(2)].

The metabolic syndrome is a cluster of cardiometabolic abnormalities which together represent added risk factors for cardiovascular disease and T2D. The syndrome occurs more commonly in overweight individuals, affecting relatively few (3–4%) young people of normal weight but depending on the definition used, 26–50% of obese children and adolescents[(3)].

Met S among school-age children is considered to be present when at least 3 or more of the following clinical and metabolic abnormalities are present together: (i) abdominal obesity, (ii) low level of high-density lipoprotein (HDL), (iii) high triglyceride, (iv) high fasting blood glucose (FBG), and (v) elevated blood pressure (BP) [(4)].

Blood pressure should be monitored at all healthcare contacts from the age of 3 years . Lipids and HDL lipid profile should be measured in overweight children between the ages of 2–8 years and repeated between 12 and 16 years old [(5)].

The pathogenesis of MS is very complex and not yet clear. Several studies support the concept that oxidant/antioxidant imbalance may play an important role in its manifestations[(6)].

Uric acid is an endogenously produced terminal degradation product of purine catabolism, formed by the liver and excreted by the kidneys primarily and intestines secondarily. Uric acid has antioxidant capacities extracellularly and can be responsible for 2/3 of the total plasma antioxidant capacity, where it chelates metals and scavenges oxygen radicals. However, intracellularly, it has pro-inflammatory and pro-oxidant activity. It has been shown that uric acid is a circulating marker for oxidative damage in conditions like ischemic liver, atherosclerosis, diabetes, and chronic heart failure [(7)].

The study aimed toinvestigate the potential association of serum uric acid (sUA) and metabolic syndrome (MetS).

II. Patients and Methods

Patients:-A prospective case-control study was conducted in Cardiac Unit, Zagazig University Children'sHospital, during the period from February 2019 till August 2019.

Our Study included:-

From 129 random obese pediatric patients according to waist circumference and BMI we enrolled 26 patients with metabolic syndrome randomly with percentage of 20.1% , and take matched control with same number.

1) Patient group: (***Group A):***

Twenty six obese prepubertal child(6-9years) patients with metabolic syndrome was diagnosed according to the criteria of International Diabetes Federation.

2) Control group ***(Group B):***

Twenty six age and sex-matched healthy children are considered a control group.

A written consent was taken from all parent of each case. The study was approved by our ethical committee.

Inclusion criteria:

- All pre-pubertal obese with metabolic syndrome according to the International Obesity Task Force (IOTF) criteria and International Diabetes Federation (IDF) criteria, (6-9 years) children attending pediatric department and not on weight loss diet.
- The International Obesity Task Force (IOTF) developed a definition for overweight and obesity in children which was based on gender and age specific body mass indices to classify children as:
  - overweight: BMI (25-29 kg/m2)
  - obese: BMI of ≥30 kg/m2 respectively.

International Diabetes Federation (IDF). According to the IDF definition, someone has the metabolic syndrome if he or she has central adiposity (waist circumference (WC) ≥ 90th percentile) plus two or more of the following four factors :

a) Blood pressure ≥ 95^{th} percentile,

b) fasting triglycerides (TG) ≥150 mg/dL,

c) high density lipoprotein (HDLc) < 40 mg/dL and

d) fasting glucose ≥100 mg/dL).[8]

Exclusion criteria:

1) Specific causes of endocrine or genetic obesity.

2) Patients with type 1 or type 2 diabetes.

3) Patients with any disease that may affect level of serum uric acid e.g: Previous heart, respiratory, liver and kidney diseases,

4) Current or past use of hormonal or interfering therapies (lipid-lowering, hypoglycemic, or antihypertensive treatments.

5) Child under the age of 6 years, or above the age of 9 years.

6) Child with sexual maturity more than Tanner stage 1.

I) <u>OPERATIONL DESIGN</u>

<u>Type of the study:</u>

A case-control study.

●***Methods***

All patients in this study were subjected to

A) *Full history taking:*

- Detailed history taking including age, sex.

B) Through clinical examination including:

1) Assessment of blood pressure: Using a mercury sphygmomanometer , the cuff length for blood pressure measurement was chosen according to the arm circumference value. Children were asked to sit for at least 5 min before measurement. Two records were taken, with 2-min interval in between, plus a further one in case of difference >5% in blood pressure between the two previous readings. The average of the two (or three) measurements was used for statistical analysis**.**The patient should be as relaxed as possible and measurement done for all subjects on their right arm**[(9)].**

2) Anthropometric measurement:

i. Weight was measured using digital scales.

ii. Height was measured to the nearest 1 cm using a non-elastic tape meter while subjects were in a barefoot standing position, with their shoulders in a normal position.

iii. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2)**[(10)].**

- Presence of obesity was determined by BMI for age using WHO Reference as follow:

WHO Child Growth Standards (birth to age 5):

❖ **Obese:** Body mass index (BMI) > 3 standard deviations above the WHO growth standard median

❖ **Overweight:** BMI > 2 standard deviations above the WHO growth standard median.

WHO Reference 2007 (ages 5 to 19):

❖ **Obese:** Body mass index (BMI) > 2 standard deviations above the WHO growth standard median.

❖ **Overweight:** BMI > 1 standard deviation above the WHO growth standard median.**[(11)].**

i. Waist circumference (WC): Is measured in the horizontal plane midway between the lowest rib and the iliac crest**.**Waist circumference (WC): Is measured in the horizontal plane midway between the lowest rib and the iliac crest **[(12)].**

International Diabetes Federation (IDF). According to the IDF definition, someone has the metabolic syndrome if he or she has central adiposity (waist circumference (WC) ≥ 90^{th} percentile) plus two or more of the following four factors :

a) Blood pressure ≥ 95^{th} percentile,

b) fasting triglycerides (TG) ≥150 mg/dL,

c) high density lipoprotein (HDLc) < 40 mg/dL and

d) fasting glucose ≥100 mg/dL)**[(8)].**

1) Biochemical measurements : Blood was collected from the antecubital vein after an 8–12 h overnight fast centrifuged within 2 h for separation of serum. Aliquoted samples were stored at −20 °C until analyses:

1. Serum Total cholesterol and TG were determined enzymatically by an autoanalyzer using commercial kits available (Beckman Coulter, Inc., CA, USA).

2. Serum HDLc was measured similarly after precipitation with magnesium phosphotungstate.

3. Serum low density lipoprotein cholesterol was calculated using Friedwald's formula as shown below.

LDL−chol ½ ¼ Total chol ½− HDL−chol ½− TG ½=5 ðÞ where all concentrations are given in mg=dL**.**[13]**.**

4. Fasting plasma glucose was measured via colorimetric assay.

5. Serum uric acid levels were determined colorimetrically using Uricase.[14]**.**

STATISTICAL ANALYSIS:A collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage , quantitative continues group represent by mean ± SD , the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X^2) . Differences between quantitative independent groups by t test, correlation by Pearson's correlation or Spearman's. A receiver operating characteristic (ROC). P value was set at <0.05 for significant results &<0.001 for high significant results. Data were collected and submitted to statistical all the following statistical tests and parameters were used .

III. Results:

- **Figure (1):** shows that from 129 random obese pediatric patients we enrolled 26 patients with metabolic syndrome randomly with percentage of 20.1%, and take matched control with same number.
- Age was distributed between cases and control as 7.52±0.91 and 7.37±0.84 respectively with no significant difference, also regarding sex distribution there was no significant difference or association regard sex distribution between groups **(Table 1).**
- **Figure (2)**: show that BMI and WC were significantly higher among cases than control
- Cases significantly higher than control regard FBS **(Table 2).**
- All parameters of lipid profile were significantly higher than control except HDL as it was significantly lower among cases **(Table 3)**.
- **Table (4) and figure (3):** show that Cases were significantly higher regard Uric acid
- All metabolic components significantly higher in cases compared with control **(Table 5)**.
- Uric acid was significantly positively correlated with BMI, WC, SBP, DBP, Fasting glucose, Triglycerides, Total cholesterol and LDL_C but significantly negative correlated with HDL_C **(Table 6).**

– Significant area under curve with cutoff >4.3 with sensitivity 70% and specificity 96.3% **(Table 7).**

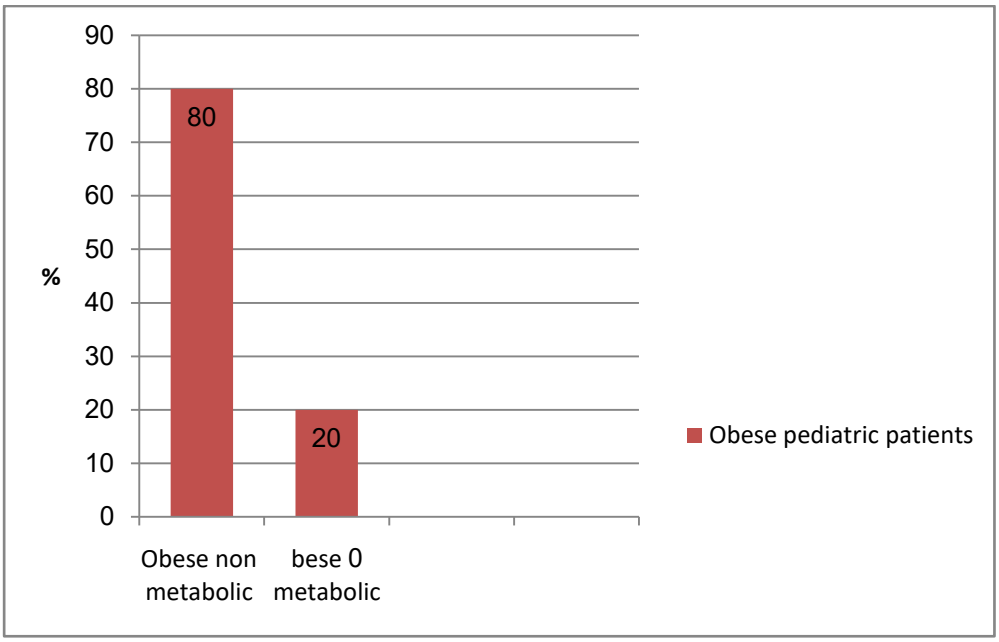

Fig (1): Percentage of metabolic syndrome patients among 129 random obese pediatric patients.

Tab (1): Age and sex distribution between studied groups

			Case (No=26)	Control (No=26)	t	P
Age			**7.52±0.91**	**7.37±0.84**	**0.613**	**0.543**
Sex	**Male**	**N**	**13**	**14**		
		%	**50.0%**	**53.8%**		
	Female	**N**	**13**	**12**	**0.077**	**0.78**
		%	**50.0%**	**46.2%**		

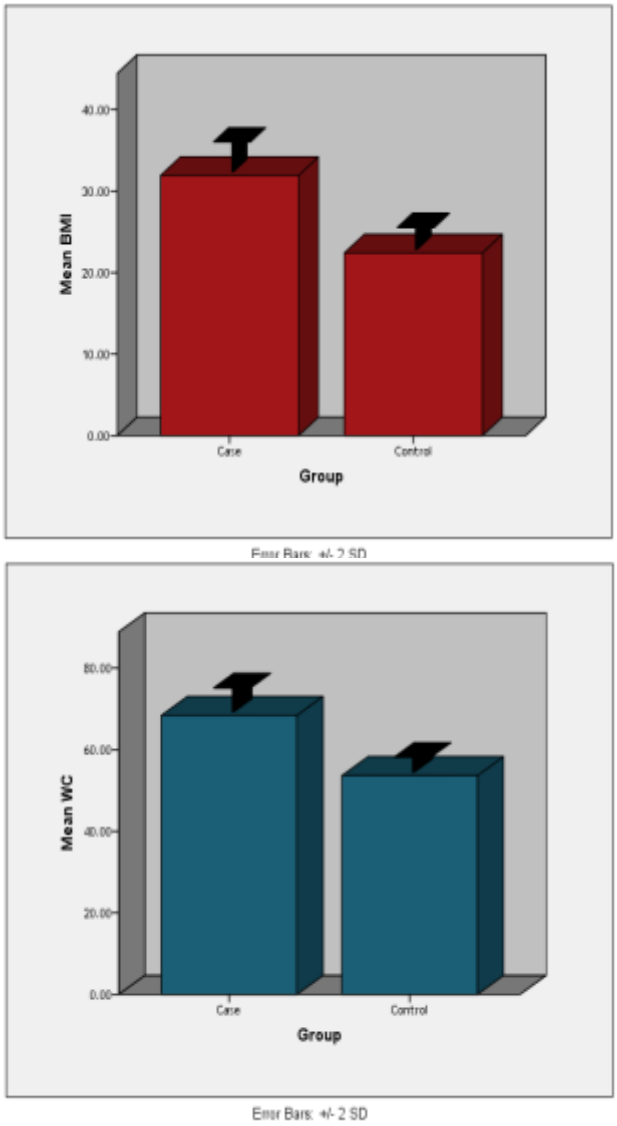

Fig (2): Anthropometric measures distribution between groups

Tab(2): Fasting blood glucose distribution between studied groups

	Case (No=26)	Control (No=26)	t	P
Fasting glucose (mg/dl)	**108.84±11.4**	**76.23±7.44**	**12.178**	**0.00****

Tab (3): Lipid profile distribution between studied groups:

	Case (No=26)	Control (No=26)	t	P
Triglycerides (mg/dl)	**122.57±28.2**	**91.31±20.27**	**4.581**	**0.00****

Total cholesterol (mg/dl)	**212.0±38.19**	**146.15±10.8**	**8.453**	**0.00****
LDL C (mg/dl)	**134.92±26.13**	**98.19±5.76**	**6.998**	**0.00****
HDL C (mg/dl)	**36.09±8.84**	**50.46±3.67**	**-7.643**	**0.00****

Tab (4): Uric acid distribution between studied groups:

	Case(No=26)	Control(No=26)	t	P
Uric acid (mg/dl)	**4.59±1.06**	**3.34±0.73**	**4.942**	**0.00****

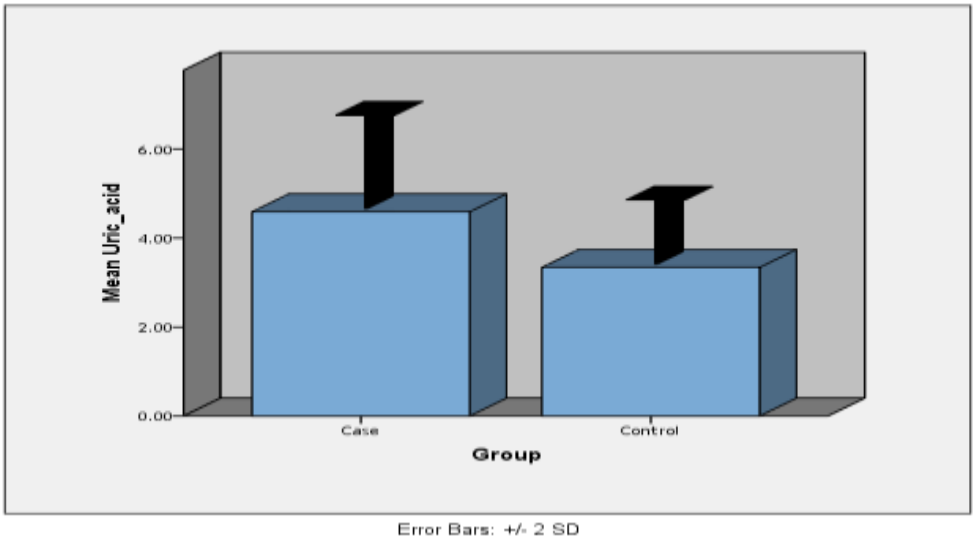

Fig (3): Uric acid distribution between studied groups:

Tab(5): Characters of metabolic components distribution between studied groups :

			Group		Total	X^2	P
			Cases	Control			
SBP2	**<95th**	**N**	**10**	**26**	**36**		
		%	**38.5%**	**100.0%**	**69.2%**		
	>95th	**N**	**16**	**0**	**16**	**23.11**	**0.00****

		%	61.5%	0.0%	30.8%		
DBP	<95th	N	10	26	36		
		%	38.5%	100.0%	69.2%		
	>95th	N	16	0	16	23.11	0.00**
		%	61.5%	0.0%	30.8%		
Fasting TG	<150	N	19	26	45		
		%	73.1%	100.0%	86.5%		
	>150	N	7	0	7	8.08	0.004*
		%	26.9%	0.0%	13.5%		
HDL_C	>40	N	9	26	35		
		%	34.6%	100.0%	67.3%		
	<40	N	17	0	17	25.25	0.00**
		%	65.4%	0.0%	32.7%		
FBG	<100	N	7	26	33		
		%	26.9%	100.0%	63.5%		
	>100	N	19	0	19	29.93	0.00**
		%	73.1%	0.0%	36.5%		
Total		N	26	26	52		
		%	100.0%	100.0%	100.0%		

Table(6):Correlation between uric acid and all studied parameters:

		Uricacid
Age	r	.128

	P	**.366**
BMI	**r**	**.615****
	P	**.000**
WC	**r**	**.495****
	P	**.000**
SBP	**r**	**.543****
	P	**.000**
DBP	**r**	**.446****
	P	**.001**
Fasting glucose	**r**	**.552****
	P	**.000**
Triglycerides	**r**	**.633****
	P	**.000**
Total cholesterol	**r**	**.668****
	P	**.000**
LDL_C	**r**	**.749****
	P	**.000**
HDL_C	**r**	**-.775-****
	P	**.000**

Tab(7): SUA as a diagnostic marker for pediatric met S; ROC curve analysis

Uric acid cut off (mg/dl)	Sensitivity	Specificity	+Ve predictive value	-Ve Predictive value	Accuracy	Area under curve	P Value
>4.3	70.0%	96.3%	0.907	0.633	95%	0.79	0.001

IV. Discussion

In our study we aimed to study SUA in MetS in pre-pubertal children (Tanner Stage I, age ≤ 9 years).

From 129 random obese pediatric patients we enrolled 26 patients with metabolic syndrome randomly with percentage of 20.1%, and take matched control with same number.Our result supported by **Fangfang et al.,**[(15)] who found that the prevalence of MetS was higher in obese than controls.

As regard demographic data,there were no significant difference between studied groups.

This came in agree with **Suhaimi et al.,** [(16)] stated that there was no statistically significant difference in the proportion of obese children with metabolic syndrome by gender.

However, **Inanc,** [(17)]reported a slightly higher prevalence of Met S in females compared to males.

Observed differences by sex may depend on the cutoffs and components used in defining MetS for example, with the IDF definition, the prevalence of MetS is slightly higher in boys than in girls. **Ekelund et al.,**[(18)] also report a higher prevalence of MetS in boys.

Our study revealed significant increase mean BMI and WC in metabolic cases than control.Our results goes with, **Bee et al.,** [(19)]who found that overweight/obese children had significantly worse clinical profiles and higher anthropometric parameters [height, weight, BMI, WC, hip circumference (HC), fat mass (FM) (%), waist hip ratio (WHR), waist to height ratio (WHtR) ,

Lee et al.,[(20)] supported that WC should be included in the evaluation of childhood obesity along with BMI percentile to identify those at increased health risks due to excess abdominal fat.

Our study showed that SBPand DBP are significantly higher among metabolic group than control one.Our results supported by**Moushira et al.,** [(21)], who reported that obese children had a significantly higher levels of systolic and diastolic BP compared to their lean controls. Similarly these findings were consistent with **Mohan et al.,**[(22)].

In our study fasting plasma glucose level (FPG) was higher in obese children with metabolic syndrome than control.This came in agree with **Maffeis et al.,**[(23)]whoexploring the clinical significance of high-normal FPG in children have been performed in obese subjects.

In our study obese metabolic cases had a significant higher lipid profile(triglycerides, total cholesterol and LDL) compared with control and significant lower level of HDL in cases than control group.

The Egyptian study done by **Moushira et al., [21]**, reported that obese children with Met S had significantly higher values of triglycerides compared to obese children without Met S, whereas HDL was significantly lower.

Augusthyet al., [24]reported that findings regarding BMI, serum triglycerides, VLDL, cholesterol/HDL ratio were significantly increased and serum HDL levels were significantly decreased in metabolic syndrome compared to controls. Also, **Gannar et al., [25]** mean levels of BMI, waist Circumference (WC), hip Circumference (HC), waist to hip ratio (Wc/Hc), SBP, DBP, glucose, triglycerides (TG), total Cholesterol (TC), LDL-C, C-Reactive Protein (CRP) were significantly increased and HDL-C levels were significantly reduced in obese subjects with and without Met S compared to controls.

Uric acid (UA) is one of the determinants of the metabolic syndrome . Individuals with high UA levels have an odds ratio of 1.6 fold higher for developing Met S. UA is associated with metabolic syndrome and its components, obesity, dyslipidemia, hypertension **[26].**

Our study showed that obese metabolic children had significantly high Uric acid compared with control (Mean SUA was 4.59± 1.06 among cases, 3.34 ± 0.73 among control).

Previous studies done by **Numata et al., [27]** have also reported higher serum uric acid level in Met S patients than compared to non MetS patients. Also, **Li et al., [28]** have found strong correlation between serum uric acid and MetS components.

Studies done in the past support this association and documented that obese subjects with raised BMI showed raised uric acid levels in addition to classical manifestations of metabolic syndrome **[29],**

Chang et al., [30] reported that elevated serum uric acid levels were contributed to higher risk of Met S.

In our study the overall, prevalence of systolic hypertension and Diastolic hypertension among metabolic cases were 61.5%, While Fasting hypertriglyceridemia were 26.9%. Moreover the overall predominance of low HDL-C in cases were 65.4% and fasting hyperglycemia in cases were 73.1%.

Nayera et al.,[31] revealed that hypertension in prepubertal was (14.8%). However, the prevalence of impaired fasting glucose (20.5%) in the pubertal group, while dyslipidaemia in the prepubertal group was 93.2%

Our results were in agreement with the study done by**Moushira et al., [21],** who showed that the prevalence of the components of Met S among obese children was as follows: abdominal obesity, 85%; high systolic BP, 8.3%; high diastolic BP, 5%; impaired fasting glucose, 8.3%; high total cholesterol, 8.3%; hypertriglyceridemia, 13.3%; high LDL, 8.3%, and low HDL-C, 20%. High frequency of high diastolic BP, triglycerides and low HDL were observed in the obese children with Met S compared to children without Met S.

In our current study, we found significantly positive correlation between body mass index (BMI), waist circumference(WC), systolic blood pressure (SBP), diastolic blood pressure (DBP),fasting blood glucose (FBG), triglycerides (TG), total cholesterol , low density lipoproteins (LDL) and serum uric acid (SUA), but significant negative correlation of serum uric acid and high density lipoprotein (HDL_C).In agreement with **Abdullah et al., [32]**show that high concentrations of plasma triglycerides are related to hyperuricemia**.**

Significant and positive correlation reported between waist circumference and uric acid levels was shown in study by **Zahid et al., [33].**

Uric acid was found to be positively correlated with serum triglyceride and negatively correlated with HDL-cholesterol levels in **Peng et al., [34]** s report.

According to ROC curve analysis, the AUC of SUA for detection of metabolic patient with best cutoff value > 4.3 with sensitivity 70% and specificity 96.3%, and this maximizing sensitivity and specificity to predict future metabolic syndrome and their area under the curve was 0.79.

An early report by **Feig and Johnson, [35]** found that a serum uric acid value > 5.5 mg/dL strongly supported the diagnosis of primary hypertension in children (sensitivity: 87% and specificity 86%).

V. Conclusion:

There was statistical significant increase in anthropometric measures, systolic blood pressure (SBP) and diastolic blood pressure (DBP), plasma glucose level (FPG),lipid profile (triglycerides, total cholesterol and LDL and Uric acid compared with control. In obese metabolic patients , there was positive correlation between body mass index (BMI), waist circumference(WC), systolic blood pressure (SBP), diastolic blood pressure (DBP),fasting blood glucose (FBG), triglycerides (TG), total cholesterol , low density lipoproteins (LDL) and serum uric acid (SUA), but significant negative correlation of serum uric acid and high density lipoprotein (HDL_C).SUA at a level of 4.3 was the best cut- off value for metabolic patients with sensitivity 70% and specificity 96.3% , and this maximizing sensitivity and specificity to predict future metabolic syndrome and their area under the curve was 0.79.Serum uric acid isa gooddiagnostic marker in metabolic syndrome children

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