



Original Research Article

Relationship between adiponectin & uric acid with inflammation in pathogenesis of metabolic syndrome

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ARTICLE INFO

Article history:

Received 13-08-2020

Accepted 06-09-2020

Available online 28-09-2020

Keywords:

Obesity

Adiponectin

Uric acid

hs-CRP

Metabolic syndrome

ABSTRACT

Background: The risk factors of Metabolic syndrome (Mets), primarily favors the development of cardiometabolic alteration, type 2 diabetes, hypertension, and dyslipidemia leading to increase in morbidity. Life style and eating habits often increases the levels of Uric acid (UA) in circulation. Elevated UA & stress, exacerbates the pain and inflammation. The inflammatory response includes systemic increase in circulating inflammatory cytokines and acute phase protein, high sensitive C-reactive protein (hs-CRP). Adiponectin (ADI) a cytokines primarily secreted by adipocytes exerts antidiabetic, anti-inflammatory & cardioprotective effects. Thus the purpose of the study is to establish a link between Adiponectin, Uric acid and hs-CRP which may further be used in diagnosis and thus can positively reverse many of the adverse effects of MetS.

Material and Methods: Present study, an observational case-control study conducted on referred MetS patients attending OPD at Chhatrapati Shivaji Subharti Hospital, Meerut. Data collected on previously validated questionnaire from 235 subjects (156 with MetS and 79 non-MetS) assessed for anthropometric measurements, diabetic profile, ADI, UA & hs-CRP were evaluated by standard established techniques.

Results: The results obtained from Mets patients were compared with non-MetS subjects, where ADI was significantly lower ($P < 0.05$) while hs-CRP & UA were significantly higher in subjects with MetS ($P < 0.01$). In Spearman's rank correlation coefficient for the relationship between ADI and metabolic variables - ADI was positively correlated with age, diastolic blood pressure, total cholesterol, HDL-C & LDL-C while negatively correlated with BMI, systolic blood pressure, fasting glucose, Triglyceride & VLDL-C. Serum hs-CRP levels were elevated with the increasing number of MetS components, being higher among those with ≥ 2 components of MetS while adiponectin decreasing with the number of MetS components. Decreased levels were reported for ADI, whereas hs-CRP & UA levels were escalating.

Conclusion: Higher levels of hs-CRP & Uric Acid with lower level of ADI associated with significantly higher risk of MetS.

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1. Introduction

An obesity and diet dependent development of MetS are considered as a global health problem. The burden of obesity on health is continuously extending across multiple organ systems and diseases.¹ With obesity, the increased production of inflammatory mediators causes subclinical metabolic inflammation.² Inflammation affects

the metabolic and secretory function of adipose tissue and plays a leading role in the development of obesity followed with MetS.³ The obese patients particularly those with visceral fat accumulation have reduced plasma ADI level, which is characteristically different from most adipokines as it is negatively correlated with obesity.⁴ Accumulating experimental evidences indicates that ADI is known to have anti-inflammatory and anti-atherogenic activities. Adiponectin due to its multiple properties

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may have a potential role in a variety of inflammatory diseases. Excessive fat accumulation in principal organs leads to inflammation characterized by an increase in pro-inflammatory cytokines. The pro-inflammatory status may lead to the clinical and biochemical manifestation of MetS.⁵ An obesity is an inflammatory state as visceral adipocytes secrete increasing amounts of inflammatory cytokines such as hs-CRP, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and chemokines. These proinflammatory conditions conferred by excess visceral adipose tissue combine to produce a tonic degree of systemic inflammation.⁶ Uric Acid (UA) end product of purine-nucleoside catabolism is a biochemical entity gaining increased importance by researchers as it is a real risk factor for the development of metabolic disorders of, renal and CVDs. The intracellular UA seems to be more pathogenic.⁷ Natural antioxidant UA correlates and predicts development of obesity, hypertension, and cardiovascular disease.⁸ Although many studies have focused on the presence and absence of an independent relationship between ADI, UA, hs-CRP & MetS, but the role & relation of all these parameters are not documented at all.

In vitro studies have shown that ADI inhibits the expression and the biological effects of TNF α , of adhesion molecules, and the macrophage-to-foam cell transformation.⁹ Recent study has supported the beneficial role of ADI in the suppression of Renin Angiotensin System-mediated vascular inflammation and macrophage accumulation; in addition, study also demonstrated that ADI increases the expression of the anti-inflammatory cytokine, IL-10 in the arterial wall.¹⁰ One more study stated that an ADI inhibits the expression of inflammation and inflammatory markers (TNF- α and IL-6) inhibits the production of adiponectin.¹¹ The protective effect of ADI was supported by human cohort studies in which hypoadiponectinemia apparently predicted the development of many diseases. However few studies reported higher ADI levels in MetS whereas some studies reported low adiponectin levels which are statistically insignificant.¹² Recently several observations suggested a potential role of ADI in variety of inflammatory diseases. Documented studies reported inverse relationships between adiponectin concentrations and proinflammatory markers.^{13,14} However few recent studies had showed that adiponectin levels and pro-inflammatory status are independent.^{15,16} Thus it is still unclear whether the higher adiponectin level is a part of the protective response to the underlying inflammation or those with low ADI are more prone for inflammation? Furthermore it is also unclear whether the decreased anti-inflammatory ADI and increased pro-inflammatory markers are associated with development of MetS? An UA has been shown to induce production of interleukins, tumor necrosis factor in human mononuclear cells in cultures of human vascular cells.¹⁷ These suggested that, UA may have a

significant interaction with high sensitive hs-CRP. Despite several reported studies it is still not clear that which role of UA is more important, mediating the effects of conventional risk factors in the development of MetS, or mediating the protective effects due to its antioxidant properties. The scenario of circulatory levels of ADI, UA & hs-CRP in Indian population has not been studied in context of MetS. This is of remarkable interest to investigate comprehensive role of these parameters in the development of MetS.

2. Materials and Methods

Present case-control study carried out on MetS patients referred from Chhatrapati Shivaji Subharti Hospital, attached with Subharti Medical Collage, Meerut underwent fasting blood glucose & lipid profile from December 2016 to February 2018. A total of 156 MetS subjects (69 male, 87 female) aged ≥ 25 years to ≤ 60 years were included in the study. Age, sex matched 79 subject (36 male and 43 female) healthy control subjects were studied, who were permanent residents of study area.

Overnight fasting 5ml venous blood samples were collected in a plain vial from study patients referred for evaluation of MetS. The serum separated & stored in aliquots in duplicates. One aliquot of each was used for the immediate assays for fasting glucose, lipid profile & Uric Acid. The other aliquots were stored at -80°C for the subsequent assays of Adiponectin, Uric Acid & hs-CRP respectively. A written consent from all the patients and control subjects obtained and followed for collection of personal data, both patient and healthy control in pre designed pretested questionnaire, which includes socio-demographic characteristics such as age, gender, occupation, socio-economic status, literacy, nationality, physical examination including pulse, blood pressure, height, weight, lifestyle habits like smoking, alcohol consumption, diet and drug history, etc. The clinical and biochemical investigations such as fasting & post prandial blood glucose, total cholesterol, HDL-C, Non-HDL-C, LDL-C levels and Triglycerides etc. were assessed by standard established techniques on Siemen's autoanalyzer.

The MetS was assessed by, IDF criteria⁸ & serum Adiponectin levels were assayed by readymade kits procured from M/S Assaypro Pvt. Ltd., USA for Human Adiponectin ELISA Kits. Uric Acid levels were assessed spectrophotometrically by enzymatic method, while hs-CRP was estimated with readymade kit procured from M/S Xema CRP Ultra EIA Company. LDL-C was calculated using the Friedewald's formula (patients with TG ≤ 400 mg/dl), whereas levels of non-HDL-C were calculated by subtracting HDL-C from total cholesterol. Height and weight were measured using standard procedure. The body mass index (BMI) was calculated as the weight in kilograms divided by height in meters square. Blood pressure was recorded using standard mercury sphygmomanometer pre-

calibrated instrument and the mean of two readings were reported five minutes apart in sitting position.

2.1. Statistical analysis

The data analyzed using SPSS statistical package software version 17. The variables expressed as Mean \pm SD, Student's t-test was used to ascertain the significance of differences between mean values of two groups. Pearson's Correlation was used to determine the correlation of MetS with risk factors. Correlation regression analyzed using same software. P-value ≤ 0.05 is considered as statistically significant.

3. Result

The present study comprises total of 235 subjects from Meerut City referred from Medical OPD, out of which 41 subjects had only 1 component, 79 subjects had 2 components, 65 subjects were with 3 components and 50 subjects had 4 components of MetS respectively. There was no significant difference in age among these four groups. On comparing patients of MetS to subjects with Non-MetS, the mean \pm SD value for ADI is 26.36 ± 3.15 ng/ml in non-metabolic group, and is significantly lower in patients of metabolic syndrome i.e. 21.26 ± 2.34 ng/ml whereas the mean \pm SD value for serum Uric Acid is 5.02 ± 0.99 mg/dl in healthy subjects and is significantly increased in patients with MetS 6.53 ± 1.49 mg/dl. Similar trend was observed in the serum hs-CRP levels of 3.33 ± 1.80 mg/L in non-metabolic group and significantly raised level 8.09 ± 4.78 mg/L in patients with MetS ($p \leq 0.001$).

The difference between values of parameter like Adiponectin, Uric Acid, Blood sugar, HDL-cholesterol, LDL-cholesterol in respect of both groups found significant i.e. $p \leq 0.05$, whereas circulatory levels of hs-CRP, BMI, B.P, Triglyceride and VLDL-C were highly significant ($p < 0.001$). The biochemical findings of control and cases shown in Table 1.

Table 2 highlights sharp decrease in serum Adiponectin levels as the number of components of MetS increases. On the other hand a strong linear increase in Serum Uric Acid and hs-CRP levels were observed with the increased severity of MetS. The trend is well illustrated in Figure 1.

The various parameters among 235 subjects were classified according to presence of number of components of MetS. Adiponectin has shown to be inversely proportional with serum Uric Acid & hs-CRP, but the difference between MetS compared to those without MetS, is highest in Group 4. There was no significant difference of uric acid levels between Group 2 & 3 as these two groups have members with significant age difference. In Group 1 (non-metabolic) with a higher concentration of ADI the level of hs-CRP and UA shows inversely proportional relation. This may be due to anti-inflammatory property of

ADI. In Group 2, 3 & 4 as with the decreasing concentration of ADI levels of hs-CRP & UA continuously increasing. Thus higher level of hs-CRP & UA with lower level of ADI were associated with significantly greater risk of development of MetS.

4. Discussion

An obesity epidemic has forced us to evaluate the role of various biochemical parameters in health complications of obesity. Abdominal obesity is the core feature of MetS. Inflammation demonstrated primarily by elevated levels of serum hs-CRP, which is thought to be associated with insulin resistance and MetS. The activation of inflammatory pathways in response to the abnormalities caused by obesity reflects the seriousness of the condition. Central obesity is considered as one of the most important determinants of low grade chronic inflammation present in MetS¹⁸. Adipose tissue secretes adiponectin a protein showing anti-inflammatory activity. Circulatory Levels of adiponectin are lower in patient with obesity, type 2 DM, arterial hypertension and MetS.¹⁵ Despite the beneficial role of adiponectin in vascular homeostasis, studies suggest that elevated circulating adiponectin associated with increased cardiovascular mortality in coronary artery diseases (CAD). Literature reports documented that elevated Uric Acid levels are commonly associated with cardiometabolic diseases. Uric Acid has even been suggested to have a protective effect due to its anti-oxidant properties. It is still not documented that, which of the following detrimental role of uric acid are more important, mediating the effects of conventional risk factors in the development of MetS, or mediating the protective effects due to its antioxidant properties.

The knowledge of pathogenesis and the factor associated with metabolic risk such as obesity, hypertension and cardiovascular risk are increasing day by day. The challenge is to translate research findings into substantial clinical improvements in patients. Adiponectin & Uric Acid levels varied depending on gender, age, ethnic background and it is therefore necessary to clarify their threshold for increased disease risk in specific groups before it considered in clinical practice. Demographic and epidemiological evidence indicates that unless an effective preventive strategy is developed, else there will be a sharp increase in the global prevalence of cardiometabolic risk factors including DM & MetS. Unfortunately, clinical therapies to treat underlying obesity often are unsuccessful hence there is an urgent need for public health measures to prevent the ongoing epidemic of MetS.¹⁹ The reframing of obesity as an inflammatory condition has had a wide impact on our conceptualization of obesity-associated diseases. Therefore in present study, we have highlighted the cellular and molecular mechanisms in development of obesity-induced inflammation. We also emphasize how defining the

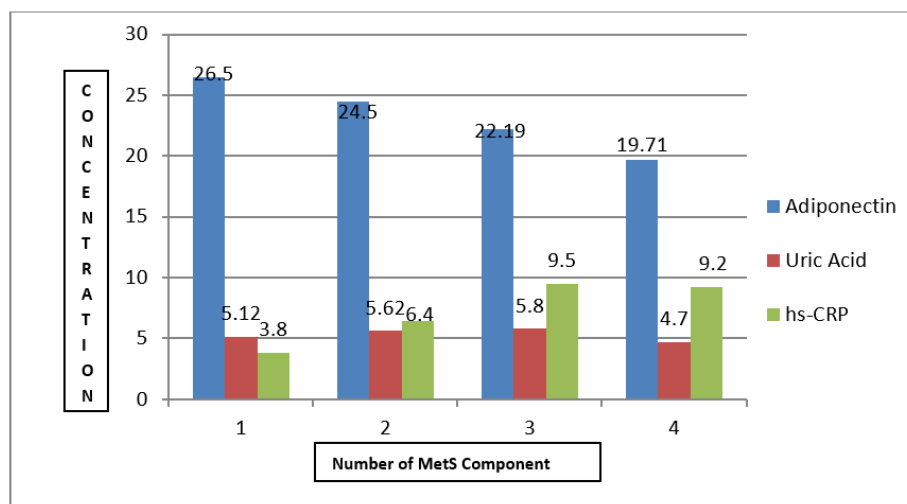
Table 1: Clinical characteristics and metabolic variables in subjects with and without MetS

S.No	Biochemical Variables	Metabolic Syndrome (MetS)		P-value
		Control (N=79)	Case (N=156)	
1	Age (Years)	41.18 ± 10.57	42.92 ± 10.28	.317 **
2	Body Mass Index (Kg/m ²)	22.12 ± 1.61	25.30 ± 2.28	< 0.001*
3	Systolic blood pressure (mmHg)	126 ± 7.96	135.59 ± 11.39	< 0.001*
4	Diastolic blood pressure (mmHg)	82.2 ± 5.39	88.31 ± 10.60	< 0.001*
5	Fasting glucose (mg/dl)	92.74 ± 7.03	109.73 ± 17.82	.002*
6	Post-prandial glucose (mg/dl)	112.86 ± 8.01	131.36 ± 14.86	.006*
7	Total cholesterol (mg/dl)	187.54 ± 24.28	200.13 ± 39.77	.668**
8	Triglycerides (mg/dl)	104.96 ± 18.30	182.53 ± 25.25	< 0.001*
9	HDL-C (mg/dl)	49.22 ± 7.92	34.03 ± 11.17	.003*
10	N-HDL-C (mg/dl)	148.32 ± 24.65	155.32 ± 39.22	.243 **
11	VLDL-C (mg/dl)	23.39 ± 5.66	42.09 ± 15.07	< 0.001 *
12	LDL-C (mg/dl)	125.15 ± 23.86	114.51 ± 35.61	.050 *
13	Adiponectin (ng/ml)	26.36 ± 3.15	21.26 ± 2.34	.013*
14	Uric Acid mg %	5.02 ± 0.99	6.53 ± 1.49	.028*
15	hs-CRP (mg/l)	3.33 ± 1.80	8.09 ± 4.78	< 0.001 *

* Significant, ** Insignificant

Table 2: Adiponectin, Uric Acid & hs-CRP levels as per frequency of MetS components

Biochemical Variables	Presence of MetS components			
	1 (n=41)	2 (n= 79)	3 (n=65)	4 (n=50)
Adiponectin (ng/ml)	26.50 ± 3.41	24.53 ± 2.41	22.19 ± 2.38	19.71 ± 2.14
Uric Acid (mg/dl)	5.12 ± 0.9	5.62 ± 1.24	5.80 ± 1.83	4.79 ± 1.05
hs-CRP (mg/l)	3.80 ± 1.83	6.42 ± 2.79	9.58 ± 6.09	9.26 ± 4.55

**Fig. 1:** Concentration of serum Adiponectin, Uric Acid & hs-CRP in presence of MetS components (group 1, 2, 3 & 4).

immune regulation in metabolic tissues has broadened the understanding of diversity of inflammatory responses. Thus presence of an obesity results in disturbances of circulatory levels of Adiponectin, Uric acid and hs-CRP, a reflection of inflammation in circulation system and their interrelation with various components of MetS are still controversial. Based on the above results, we conclude our present study that there is a possible associations of Adiponectin with UA, & their relation with degree of inflammation (hs-CRP) in patients suffering from of MetS.

Present Study highlights ADI was significantly lower ($p < 0.05$) in non MetS group, while hs- CRP and UA were significantly higher ($p < 0.01$). Pearson's correlation coefficient relationship where ADI was positively correlated with age, diastolic blood pressure, total cholesterol, HDL-C & LDL-C respectively & was negatively correlatively with BMI, systolic blood pressure, fasting glucose, Triglyceride, VLDL- C & hs-CRP levels were elevated with increasing number of MetS components.

5. Conclusion

Present study highlights the prevalence of MetS with IDF criteria in western U.P adolescent population. The high prevalence around the age of puberty. Immediate lifestyle modifications are urgently needed to control the obesity epidemic and its metabolic consequences. Accordingly to our study subjects suffering from MetS may have a higher inflammation status as well as Uric acid. A higher inflammation status was significantly correlated with decrease in the levels of Adiponectin and an increase in the risk of MetS. Further, research is needed to know the effects of obesity and its immediate as well as late consequences on MetS. The knowledge of pathogenesis and the factors which are associated with metabolic risk such as obesity, hypertension, and cardiovascular risk are increasing day by day. The challenge is to translate research findings into substantial clinical improvements in patients. Demographic and epidemiological evidence indicates that unless an effective preventive strategy is developed, else there will be a sharp increase in the global prevalence of cardiometabolic risk factors including DM and MetS. Unfortunately, clinical therapies to treat underlying obesity often are unsuccessful. Lifestyle measures have been shown to improve insulin resistance, insulin secretion and various components, effects of MetS, hence there is an urgent need for public health measures to prevent the ongoing epidemic of MetS.

6. Source of Funding

None.

7. Conflict of Interest

None.

Acknowledgment

Authors would like to thank participating subjects both control and patients in the present study.

There is no conflict of interest among authors. The study was self-funded and approved by Institutional ethical committee of Swami Vivekanand Subharti Medical College, Meerut.

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Cite this article: Adhikari P, Nagtilak S, Parashar P. Relationship between adiponectin & uric acid with inflammation in pathogenesis of metabolic syndrome. *Int J Clin Biochem Res* 2020;7(3):343-348.

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