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Effect of Increasing Body Mass Index On the Activity of Matrix Metalloproteinase-2

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Abstract: The Increasing Body Mass Index is one of the major concerns in today's lifestyle, which may give rise to various disorders. Studies have suggested that Matrix Metalloproteinases (MMPs) are associated with Obesity and cardiovascular disease. This study aimed to evaluate the serum activity of Matrix Metalloproteinase-2 in overweight patients with anthropometric measurements to assess the effect of body mass index in MMP-2 activity. In this Age and sex matched case-control study the participants were selected in 2:1 ratio (219 cases and 108 controls). In this study Body Mass Index, Blood Pressure, and other biochemical parameters i.e. Fasting Blood Sugar (FBS), Total Cholesterol (TC), Triglycerides (TG), High-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C) along with MMP-2 were measured through semi-autoanalyzer and ELISA respectively. There was an increased concentration of FBS in overweight patients compared to the control group, which was statistically significant. In the case of lipid profile, there was an elevated concentration of TC, TG, and LDL-C in the overweight population when compared to the control group and the findings were statistically significant, while HDL-C was significantly elevated in the control group compared to the case group. With respect to blood pressure, a significant increase was observed in systolic and diastolic blood pressure. In this study, there was a significant elevation of MMP-2 in the case group compared to the control group, which was positively associated with Body Mass Index. The outcome of this study revealed that increasing body weight might be the root cause of developing several life-threatening risk factors if not considered at initial level. Furthermore, altered concentration of MMP-2 in overweight patients may highlight cardiovascular Risk in these patients.

Keywords: Body mass index, MMP-2, Obesity, Extracellular Matrix and Hypertension.

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1. INTRODUCTION

Weight gain is now recognized as a global public health problem. This is associated with the overgrowth of adipose tissue and hypertrophy of fat cells in the body.[1] Gaining weight can cause a chronic illness called Obesity. This is caused by lifestyle behaviors such as lack of exercise, high sugar intake, and a fat diet. Excessive food, genetics, and several illnesses such as hypothyroidism, insulin resistance, and polycystic ovary syndrome also contribute to the progression of Obesity.[2] The study aims to evaluate the activity of Matrix metalloproteinase-2 in the progression of body mass index from overweight to Obesity. In 2016, WHO estimated that more than 1.9 billion adults (39%) worldwide were overweight and more than 650 million (13%) were obese. The prevalence of Obesity varies from country to country and from zone to zone. The prevalence of Obesity in India is 40.3%. It is highest in the South Zone (46.51%) compared to the East Zone (32.96%)[3]. Obesity is a risk factor for non-communicable diseases such as hypertension, type 2 diabetes, heart disease, stroke, certain types of cancer (endometrium, prostate, breast, ovary, liver, gallbladder, kidney, colon) and osteoarthritis.[4] The growth of fat cells accompanied by obesity. Besides their metabolic activities, Adipocytes can produce several factors, such as growth factors and cytokines, which may play a role in the paracrine regulation of the adipose tissue remodeling proteases and ECM components might also have an essential function in regulating adipose tissue remodeling. Matrix metalloproteinases (MMPs) may contribute to tissue remodeling by degradation of ECM and basement membrane components or activation of latent growth factors. Elevated levels of cytokines and growth factors can also affect the activity of matrix metalloproteinases (MMPs). It plays a central role in controlling fat production through the proteolytic activity that occurs during increased fat mass[5,6]. MMPs, can break down protein i.e collagen, normally present in the space between cells in tissues, and are a serum marker of vascular disease.[6] These are involved in physiological and pathological complications of Obesity through the degradation and remodeling of extracellular matrix (ECM) molecules.[7] MMPs activity is regulated by the Tissue Inhibitor of Metalloproteinases (TIMPs). Any changes in MMPs and TIMPs levels can result in various pathological conditions[8]. In these MMPs, high expression of MMP-2 was reported in adipose tissue of mice with nutritionally induced Obesity as well as genetically mice.[9] The Study suggests that MMP-2 has high activity in human adipose tissues compared to the MMP-9. This data indicates that MMP-2 could be an important key regulator of adipocyte differentiation[5,6]. MMP-2 and MMP-9 are both involved in the remodeling process by destroying the basal membrane and ECM components, resulting in the accumulation of lipids and adipose tissue expansion.[10] For this reason, MMP-2 is highly expressed in vulnerable regions of atherosclerotic plaques; therefore, it might be involved in plaque rupture. Recent data suggest a direct role of adiponectin in atherosclerotic plaque stability through interaction with MMPs and their inhibitors[11]. Obesity represents a cardiovascular risk factor, and the role of MMPs as modulators of adipogenesis in humans remains poorly clarified, so we hypothesized changes in ECM through MMPs might play a critical role in the adipocyte differentiation process in which we evaluate the serum concentration of MMP-2 in overweight as well as in obese subjects.

2. MATERIALS AND METHODS

2.1 Study Design and Patients

This cross-sectional study was conducted in the Department of Biochemistry in "Rohilkhand Medical College & Hospital Bareilly". The participants, selected only based on body mass index ≥ 25kg/m^2 (World Health Organization 1997) with the age range 18-45 years, were found to be in good health based on personal questionaries, physical examination, and medical history or family history. The study excluded people with familial or severe dyslipidemia (triglycerides and total cholesterol above 300 mg/dl), as well as people with a family or personal history of hypertension or who had previously been treated with drugs Factors like alcohol and smoking, which may influence cardiovascular Risk, were also excluded from the study. In addition, conditions that could affect the plasma level of MMP-2, such as pulmonary fibrosis, hepatic fibrosis, rheumatoid arthritis, recent surgery, pregnancy, postmenopausal women or steroid use, were also excluded from the study. These participants were compared to 108 age and gender-matched normal healthy individuals (25kg/m2) who served as the control group. This study was ethically approved (BIU/REG/PhD/321) by the institutional ethical committee of Rohilkhand Medical College. This research was conducted according to Helsinki guidelines and informed consent was obtained from all participants.

2.2 Assessments

Before starting the study, all participants underwent an initial screening assessment that included a medical history, physical examination, and measurements of body mass index (BMI), waist circumferences (WC), blood pressure (BP), fasting blood glucose (FBG), blood pressure, lipid profile and MMP-2. Body mass index was measured by using each individual's height and weight. The participant's height was measured using a stadiometer without shoes, and weight was measured using a digital weight machine wearing light clothes.[12] The Body Mass Index (kg/m^2) of a person was calculated by dividing weight in kg by the square of height in meters[13]. Waist circumference (WC) was measured at the midway point between the lower rib margin and the crest of the ileum in a horizontal plane at a standing position (cm) [14]. Participants were asked to sit in relaxed position before taking blood pressure which was estimated by means of the auscultatory method using sphygmomanometer from the left arm of the participants[15]. All parameters were determined after 12-h overnight fast. Venous blood samples were taken for all patients in the morning and were drawn from an antecubital vein with a 19-gauge needle without venous stasis. A blood sample was taken in a plain vial (red), 1mg/ml, and centrifuged at 3000 ×g for 15 min. Immediately after centrifugation, the serum samples were frozen and stored at -20°C for less than 3 months. All measurements were performed in the biochemistry laboratory. Fasting blood glucose was measured by the glucose-oxidase method (GOD/PAP; EM-360 Erba TRANSASIA BIO - MEDICALS LTD India)[16]. Total cholesterol (TC) and triglycerides (TG) levels were determined using fully enzymatic techniques on a clinical chemistry analyzer (CHOD-POD and GPO-PAP method respectively EM-360 Erba TRANSASIA BIO- MEDICALS LTD India). High-density lipoprotein cholesterol (HDL-C) level was measured . CHOD-POD/Phosphotungstate Method, and low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald formula[17]. MMP-2 level was determined by two-site ELISA

methods using commercial reagents (Cat. No E0904Hu, Bio Assay Technology, Shanghai Korain Biotech, China). The intra- and inter assay CsV for measuring MMP-2 levels were 8%, and 10%, respectively.[18]

3. STATISTICAL ANALYSIS

All the baseline parameters of overweight and enzymatic marker tests were presented in Mean±SD. Mann Whitney U test was used to compare two independent groups. An analysis of Variance (ANOVA) was applied to test different parameters among the groups. The Chi-square test was applied to differentiate various parameters between the subdivision of the cases. A Pearson correlation coefficient was used to the association of BMI and MMP-2 in overweight patients. A p-value less than 0.05 were considered statistically significant. A statistical software IBM-SPSS (Statistical package for social science) Version 23.0 was used for statistical analysis.

4. RESULTS

4.1 Study Sample

Total 219 participants were recruited [19]on the basis of BMI (>25kg/m^2) for the study in which 111 were females and 108 males and compared with 108 normal healthy controls in which 48 were females and 60 were males. The demographic and clinical characteristics of both groups were summarized in Table-1.

4.2 Anthropometric Parameters

The BMI and WC were increased and the p-value was <0.001, which is significant in the overweight group as compared to controls. Results are reported in Table 1.

4.3 Blood Pressure Control

SBP and DBP variations were obtained in an overweight group with respect to controls, as reported in Table 1.

4.4 Glycemic Control

Fasting blood glucose level was also increased in overweight subjects when compared to the controls. A significant p-value (<0.001) was obtained. (Table 1)

4.5 Lipid Profile

TC, LDL, VLDL, and TG were increased in overweight groups when compared to the controls which is significant, whereas HDL reduces in the overweight group as compared to controls. (Table 1)

4.6 Enzymatic Characterization

MMP-2 level quantified in control and overweight groups are reported in Figure 1. MMP-2 level was significantly higher in an overweight group than in control subjects (p < .0001). Table-2: The ANOVA test was done in which the subdivision of the case group into overweight and obese group and compared with the control group shown in table -2. The WC was statistically significant in both groups when compared with the control group. Some variations were also observed in the systolic and diastolic blood pressure in these groups. The Fasting blood sugar was significantly changed in overweight as well as obese when compared with the controls. The lipid parameters i.e. TC, TG, LDL, and VLDL level were elevated in both groups except HDL when compared with the control group which is statistically significant. The enzymatic parameter, MMP-2 was also observed as a highly significant value in the overweight as well as an obese group when compared to the control group. Table-3: The various parameters were tested on basis of subdivision of the cases into two groups. In group 1 we select 157 cases in which the BMI was ≥ 25kg/m^2 to ≤ 30kg/m^2 on the other hand in group-2 having 62 cases in which a BMI ≥ 30kg/m^2. In this study 91 cases in group 1 and 34 cases in group 2 were found to be having increased concentration of fasting blood sugar level (>126mg/dl). On the other hand, we obtained very few cases i.e., 68 and 24 in group-1 and group-2 respectively having a high blood pressure which is more than >140/90 mmHg. Similarly, 98 out of 157 and 38 out of 62 cases were found to be having increased triglycerides concentration (>150mg/dl) from group 1 and group -2 respectively. In Table 4: The positive association of Body Mass Index with the matrix metalloproteinase-2 was found in the study population which is highly significant (p <0.0001).

Table 1: Data at baseline in control and obese group

	Controls	Case
N	108	219
Age	39.83±14.76 37.0[27.0-55.0]	44.1±10.6 42.2[38.0-52.0]
BMI (kg/m^2)	20.3±2.5 20.0[18.4-22.4]	29.5±4.31 29.0[26.8-31.0] *
WC (cm)	83.2±9.2 83.0[73.0-91.0]	100.3±12.2 97.0[93.0-107.0] *
SBP (mmHg)	129.6±16.0 130.0[120.0-136.0]	136.7±13.8 135.0[132-142] *
DBP (mmHg)	83.0±9.5 85.0[77.0-88.0]	88.5±7.3 88.0[83.0-95.0] *
FBG (mg/dL)	109.30±14.38 109.0[101.0-118.0]	125.4±46.5 115.0[102.0-132.0] *
TC (mg/dL)	186.48±28.13 184.0[168.0-200.0]	202.6±31.8 205.0[184.0-212.0] *
LDL (mg/dL)	111.70±18.89 109.2[98.1-122.0]	119.9±29.4 115.2[105.4-127.8] *

VLDL (mg/dL)	25.93±9.58 25.2[17.8-30.4]	31.0±7.0 32.0[25.0-36.0] *
HDL (mg/dL)	48.28±6.33 48.0[44.0-52.0]	43.92±2.87 44.0[42.0-46.0] *
TG (mg/dL)	129.69±47.96 126.0[89.0152.0]	155.2±35.2 161.0[128.0-184.0] *

Table 1 illustrates the anthropometric measurement, FBS and lipid profile between control and case group by using Mann whitney U test. In case group except Age and HDL-C, all the parameters were significantly increased (<0.001) compared to control group. This table describes that increasing body weight is significantly responsible for developing diabetes, hypertension and dyslipidemia.Note. Data are mean ± SD and median [interquartile range]. *p< .0001 versus controls. BMI: body mass index; WC: waist circumference; FBG: fasting blood glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; Tg: triglycerides.

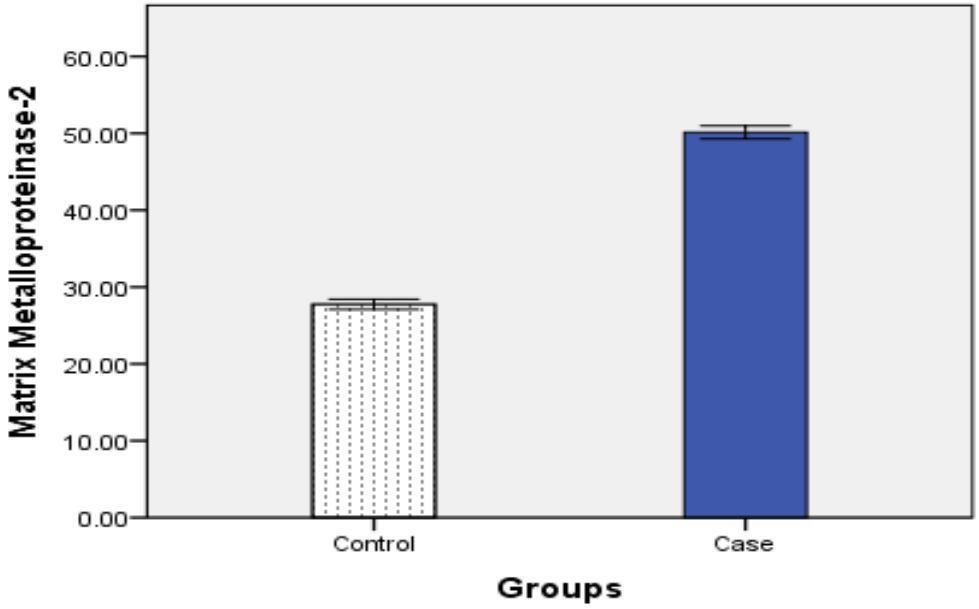

Fig. 1. illustrates that the MMP-2 concentration

Expressed in Mean±SD, was significantly higher in case group when compared with control group (<0.001) MMP-2 activity has been found to be increased in many cardiovascular pathologies e.g. myocardial infarction, hypertensive heart diseases, where tissue remodelling and inflammatory response is unsettle. Therefore, its increased concentration in case group may be harmful with progression of disease.

Table 2 : Presentation of various parameters in different groups

S. No.	Variables	Controls (108)	Overweight (157)	Obese (62)	F Value
1.	WC	83.29±9.29	96.42±9.47	110.14±13.34	139.11*
2.	SBP	129.60±16.09	134.53±11.85	143.06±17.37	16.99*
3.	DBP	83.05±9.55	88.31±6.56	89.29±9.41	16.68*
4.	FBS	109.30±14.38	116.45±18.97	142.37±72.50	18.28*
5.	TC	186.48±28.13	200.33±30.90	205.06±32.85	9.56*
6.	LDL	1121.70±18.89	117.99±23.07	121.56±38.78	3.36*
7.	VLDL	25.93±9.58	30.78±6.90	30.80±7.53	13.32*
8.	HDL	48.28±6.33	44.84±2.47	41.58±2.47	53.31*
9.	TG	129.69±47.96	153.92±34.51	154.01±37.66	13.30*
10	MMP-2	27.75±3.54	49.76±6.19	51.06±6.42	596.74*

Table-2 illustrates that the various parameters discussed in this study were statistically significant (<0.001) when compared within subgroups by using analysis of variance (ANOVA). Anthropometric measurements were found to be significantly higher in overweight group followed by obese group. FBS was significantly lower in overweight patients followed by control groups. Lipid profile (except HDL-C) and MMP-2 were also presented with similar findings that were comparatively higher in overweight patients and highest in obese patients, which may promote the development of cardiovascular disease .

Table 3: Various parameters in Case group

Parameters	Yes/No	Group 1 (157)	Group 2 (62)	Chi-Square
Fasting blood sugar (>126mg/dl)	Yes	91	34	0.177
	No	66	28	
Blood Pressure (>140/90mmhg)	Yes	68	24	0.387
	No	89	38	
Triglycerides (>150mg/dl)	Yes	98	38	0.024
	No	59	24	

Table-3 illustrates that in case group various parameters including FBS (>126mg/dl) for developing diabetes mellitus, Blood pressure (>140/90mmHg) for developing hypertension, and triglycerides (>150mg/dl) for developing dyslipidaemia, were calculated, which has also been emerged as contributing risk factors for developing cardiovascular disease. FBS level >126 mg/dl was found in 125 patients, in which 91 patients were overweight, and the remaining 34 were obese. Likewise, out of 92 patients with blood pressure >140/90mmHg, 68 were overweight and other 24 were obese. Similarly, increased triglyceride level >150 mg/dl was found in 136 patients out of which 98 were overweight and 38 were obese.

Table-4 Association between Body mass index and matrix metalloprotein-2 in case group

S. No	Parameters	r value	p value
1	BMI-MMP-2	0.295	<0.0001

Table-4 describes the positive association of MMP-2 with BMI in case group by using pearson correlation coefficient and the findings were statistically highly significant (<0.001) this finding confirms that the concentration of MMP-2 increases with a simultaneously increase in BMI. MMP-2 has been involved in physiological and pathological complications of Obesity through the degradation and remodeling of extracellular matrix molecules.[6]

5. DISCUSSION

Obesity is a global health issue that has the potential to accelerate the progression of heart illnesses in the future. Increased levels of SBP and DBP observed in the overweight group when compared with the control group in this study support the fact that increased BMI may contribute to vascular and systemic insulin resistance, as well as sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system dysfunction (RAAS). Obesity-related hypertension is also influenced by structural and functional changes in the kidney, such as the activation of intrarenal angiotensin II (Ang II).[20] Furthermore, there was an increase in fasting blood sugar concentration in overweight and obese patients in this study, which was supported by Schnurr TM et al. study, which concluded that Obesity had a greater impact on type 2 diabetes risk than other risk variables, emphasizing the importance of weight management in type 2 diabetes prevention. [21] In support of this, Agrawal N observed a positive association between body mass index and fasting blood sugar[22]. According to Kotsis V et al, plasma renin activity, angiotensinogen, angiotensin II, and aldosterone levels all rise significantly during Obesity. Insulin resistance and inflammation may promote an altered profile of vascular function and, as a result, hypertension.[23] This could explain why the case group's blood pressure is higher than the control groups, leading to hypertension in this study. Moreover, Yudin R et al concluded that Obesity based on BMI is related to HDL-C and TG when they observed the lower concentration of HDL-C and higher concentration of TG in obese patients similar to this study.[24] The pathophysiology behind Obesity is multifactorial, including hepatic overproduction of VLDL, decreased circulating TG lipolysis and impaired peripheral FFA trapping, increased FFA fluxes from adipocytes to the liver and other tissues, and the formation of small dense LDL in the case group compared to the control group in this study.[25] Ranganathan S, et al. concurred with these findings, stating that people with high BMI had a higher risk of dyslipidaemia than those with normal BMI.[26]Because there were several metabolic syndrome factors present, such as atherosclerosis, myocardial infarction, and cardiac dysfunctions, which could add to future CVD risk. According to several studies, MMPs have been implicated in the pathogenesis of atherosclerotic plaque and Obesity, both of which are significantly linked to CVDs. MMP-2, in particular, degrades collagen type IV, a key component of the basement membrane that aids in skeletal muscle cellular organisation.[27] MMP-2 is secreted by adipose tissue, and its activity is controlled during adipose tissue expansion and regression, according to recent research.[28] In this study, there was an increased concentration of MMP-2 in the case group when compared to control group. MMP-2 is highly expressed in adipose tissue, according to V. Miksztowicz and Soumaya Boumiza, who discovered a high level of MMP-2 in obese individuals.[11,7] Similarly, Derosa G et al and Gregorio Caimi, also examined a higher concentration of MMP-2 and MMP-9 in obese population when compared to the control group while supporting to this study[6,29]. According to the study of Vanessa A. Belo, they observed a higher concentration of MMP-2 in hypertensive obese children.[30] Similarly the study of Fréderic Mota also expressed the higher activity of MMP-2 in overweight and obese people as compared to the normal weight controls.[31] In this investigation, we also discovered a high concentration of MMP-2 in the Case group compared to the control group. In this study, there was a strong association between BMI and MMP-2 in study population. But still previous studies are also controversial. The findings suggested there is no risk to definite risk[32-,34].

6. LIMITATIONS

1. The only limitation of this study was the parameter since in this study, only one parameter MMP-2 was investigated. So other parameters e.g., MMP-8 and MMP-9 with increased sample size might be used to establish the fact.
2. Another limitation of this study was diabetes risk assessment because in this study HbA1c and insulin resistance were not investigated which might be used for better assessment of diabetes.

7. CONCLUSION

This study shows that overweight or increasing BMI patients may lead to the progression of Obesity and alteration of the marker MMP-2. All of these together invite many complications like hypertension, diabetes mellites, and cardiovascular diseases, which influence morbidity and mortality. So, increasing BMI cannot be ignored since it may be responsible for many complications. Increased level of MMP-2 in Overweight and increased BMI is critical because this involves an early stage of cardiovascular disease, measurements of soluble molecules may improve the Risk of assessment, early diagnosis, and prognosis of cardiovascular disease.

8. AUTHORS CONTRIBUTION STATEMENT

Richa Jain did the practical work and prepared the manuscript. Dr Biswajit Das finalized the theme of the manuscript and provided valuable guidance during the preparation of this manuscript. Dr Shikha Saxena shared her experience in writing the manuscript and finalized the writing work. Dr Gaurav Gupta supported in the material and methods and also helped in statistical analysis.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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