CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3589973

Available online at: http://www.iajps.com *Research Article*

ROLE OF INFLAMMATION IN OBESITY & DIABETES MELLITUS

Dr Syeda Ijlal Zehra Zaidi[1], Dr Naghmana Lateef[2], Dr Farhat Ijaz[3], Dr Shaheena Naz[1], Dr Rana Khurram Aftab[5], Dr Sumera Saghir[1]

[1]Avicenna Medical College, Lahore
[2]Fatima Jinnah Medical University, Lahore.
[3]CMH Lahore Medical College (NUMS), Lahore.
[4]Ex King Edward Medical University, Lahore

Abstract:

Background& Objectives: *Obesity which is an alarming medical disorder usually presented with inflammation of low grade is documented to be associated with elevated level of C-reactive protein (CRP), a renowned protein of acute phase produced by the liver. We conducted this study to correlate the likely inflammatory role in obese diabetic and non diabetics.*

Methods: *We measured serum glucose in fasting state of 6-8 hours; serum insulin and levels of CRP in forty obese diabetics with BMI of 35 ± 5 kg/m^2 and forty non diabetics obese with BMI of 33 ± 3 kg/m^2. Model of HOMA IR was used to assess insulin resistance. Data was presented as mean with standard deviation of every parameter of the current study. P value less than 0.05 was reflected statistically significant.*

Results: *We noted noticeably raised Body mass index BMI, level of C reactive protein fasting blood glucose, insulin resistance amongst the diabetics as compared to controls. Analysis through Pearson's correlation test exposed significant positive correlation amongst BMI, HOMA-IR and CRP in obese diabetics. Likewise, a less noteworthy relationship also existed between all these parameters in obese non diabetics*

Conclusion: *We concluded that noteworthy association occurs amongst insulin resistance and inflammatory marker CRP in obese diabetics having T2DM.*

Key Words: *Obesity, Inflammation, Diabetes Mellitus, C-reactive protein, Body Mass Index*

Corresponding author:

Dr. Farhat Ijaz,
Assistant Prof of Physiology, CMH LMC
Email: farhat_khurram_rana@cmh.edu.pk
.

QR code

Please cite this article in press Farhat Ijaz et al., ***Role Of Inflammation In Obesity & Diabetes Mellitus.,*** *Indo Am. J. P. Sci, 2019; 06(12).*

INTRODUCTION:

Obesity is a medical disorder that arises when a person either carries extra weight or body fat. Obesity which is documented as an epidemic disaster in United States is defined as having a body mass index of 30 or more [(1)]. Though BMI takes into account persons weight & height but according to centers for disease control & prevention (CDC) BMI has some limitations of factors like age, gender, ethnicity & muscle mass which deeply influence [(2).] In spite of these restrictions, BMI is still considered to be widely used as an indicator of excess weight [(3)]

C reactive protein which is product of the liver is a well known indicator of systemic inflammation. C-reactive protein is a delicate symbol of systemic inflammation which has conventionally been used to identify injury infection of acute phase and inflammation [(4)] Though CRP is not a diagnostic test for Heart disease yet one study found that CRP level is a better indicator of CVD than the LDL test. Long standing inflammation of low-grade with high assembly of proteins of inflammation is thought to be associated in Type 2 diabetes mellitus (T2DM) development [(5)]. Raised high-sensitivity C-reactive protein is a potential reason of the etiology and manifestation of type 2 diabetes, even though the precise mechanisms are yet to be fully understood. C Reactive protein is documented to be a prime marker of inflammation linked with T2DM .Though it is taken to be non specific indicator of inflammation yet it is now considered to be an important risk factor for diabetes to develop (T2DM) [(6)]

Type 2 diabetes mellitus is long lasting ailment which is reflected to be prominent health problem all across the world, prevalence of which grew within past thirty five years from about 108 million in 1980 to about 422 million in 2014 and incidence of T2DM is projected to rise to 552 million by 2030 [(7)] Number of people having diabetes is on fast increase because of various factors like heavy growth of population, more settlement of people in urban areas, lack of physical activity, ageing of the population and most importantly obesity [(8)]Diabetes Mellitus remains to be the leading & one of the most important health related problems of 21st century. It is normally associated with obesity and other various abnormalities of metabolism like elevated triglycerides, low density lipo-protein cholesterol & central obesity

Obesity itself leads to some degree of inflammation & insulin resistance so normally T2DM arises in obese persons. It was documented by American Diabetes Association that majority of obese persons improve insulin resistance upon loosing weight but it is unlikely that they will ever recuperate normal levels of blood glucose [(9).] Furthermore Votey & Peters noted that though insulin resistance was present in all overweight individuals yet chances of developing diabetes will be when their beta cells will weaken to function [(6)]. In a study done by Khadori et all, it was found that more than 90 % of patients having BMI greater than 30 progress to T2DM [(10)]

Researches done in the past anticipated that inflammation resulting from dysfunction of beta cells shows a weighty role in the pathogenesis of diabetes mellitus & those researches relate diabetes with reactions of inflammation. In almost all inflammatory conditions, IL- 6 is expressed in adipose tissue which controls the CRP expression in hepatocytes at level of transcription. Thus it was proved that in the diabetes mellitus & metabolic syndrome, chronic systemic inflammation has been well recognized as an associated factor [(11, 12)]

In a study by Charrier et al., potent phagocytic activity was recognized by the adipocyte precursors which can be transmuted into macrophage like cells in the reply of suitable stimuli [(13)] This impression was additionally reinforced by Lehrke et al who witnessed pre adipocytes, trans segregating into macrophages.[(14)] Macrophages & Adipocytes hold alike characters, like activation of complement and creation of inflammatory cytokines, thus proving a prominent connection between biology of adipocyte and macrophage [(15)]

Inflammatory mediators such as tumor necrosis factor α and interleukin 6 are released by the presence of additional macronutrients in the adipose tissues which in turn stimulates the liver to produce and discharge C-reactive protein [(16)]
Insulin stimulated phosphorylation of IRS-1 is greatly affected by CRP which in turn disrupts metabolism of glucose by harming signaling pathway of insulin which normalize transport of glucose at cellular level [(17)]. Furthermore Prayenac et al noted that uptake of glucose influenced by insulin & glucose integration into muscle glycogen is greatly influenced by CRP [(18)]C reactive protein also encourages oxidative stress in the skeletal muscle & liver thus aggregating the danger of diabetes mellitus. Different epidemiological researches have exposed an association amongst obesity, elevated CRP levels and insulin resistance [(19, 20)]. So from the above discussion it is found that a better & clear understanding of the pathogenesis of type 2 diabetes mellitus including its interface with inflammatory

responses may deliver a better perception into avoiding its complications. Therefore we conducted this study to find correlation amongst obesity and Inflammation in obese type 2 diabetics and non diabetic subjects.

METHODOLOGY:

We conducted this study in the Physiology department of Ameerudin medical college /Postgraduate Medical Institute Lahore in cooperation with the Medicine department of Lahore General Hospital after taking approval from Ethical Committee of Postgraduate Medical Institute affiliated with Lahore General Hospital. We enrolled eighty obese subjects with BMI greater than 30, having ages in between 35-55 years. Obese persons having any inflammatory disease, diabetic family history and gestational diabetes were excluded from our study. Out of 80 obese persons enrolled in our study, forty subjects were newly detected diabetics enrolled from LGH diabetic Clinic while forty non diabetic controls were recruited from the helpers of the patients

We took written informed consent from each subject to participate in the study. We explained risks & purpose of the study to all eligible subjects. A case report form was designed to get personal information according to the recruitment criteria of our study. After getting basic information we recorded body weight and height of all obese subjects in fasting state of 6 hours wearing light clothes and without shoes.
We drew 5ml of fasting blood sample and estimated glucose by glucose oxidase method on the similar day while serum was stored at minus 80^0C till it was evaluated. Human insulin and CRP were estimated by ELISA assays.

We determined mean and standard deviation of each parameter. Student's t test was used to check the significance of differences among the diabetic and non-diabetic group. Pearson correlation coefficient was used to conclude correlation between body mass index, blood glucose, serum insulin and HOMA-IR. p value less than 0.05 was considered statistically significant

RESULTS:

80 obese subjects divided in 2 groups, 40 diabetic & 40 non diabetic. Mean age of our patients in diabetic group was found to be 44±7 years including 28 females (70%) and 12 (30%) males while mean age of the patients in non diabetic group was 40±6 years having same number of females & males. There was a statistically significant difference between ages of cases & controls p=0.012. Mean age did not show any confounding effect or interaction in the logistic regression model. Mean BMI ± of diabetics was 35 ± 5 kg/m2 while in controls it was found to be 33 ± 3kg/m2. A statistically significant difference (p=0.032) was noted between the 2 groups

Fasting blood sugar was significantly higher (p=0.0001) in cases (164± 46) than in controls (83±8). Similarly serum insulin levels were also found to be significantly higher (p=0.0001) in diabetics (37 ± 7) than in controls (26 ± 6). Moreover HOMA-IR calculations showed that T2DM subjects had a significantly increase (p=0.0001) in cases (19 ± 8) as compared to normal subjects (5 ± 1). Statistically significant difference in serum CRP levels was also noted in diabetics (2 ± 0.17) than in non diabetics (1 ± 0.20). At Pearson's correlation analysis, a significant positive correlation was found amongst insulin resistance and inflammatory marker CRP in obese subjects having T2DM

ANTHROPOMETRIC CHARACTERISTICS IN OBESE DIABETIC & OBESE NON DIABETIC GROUPS

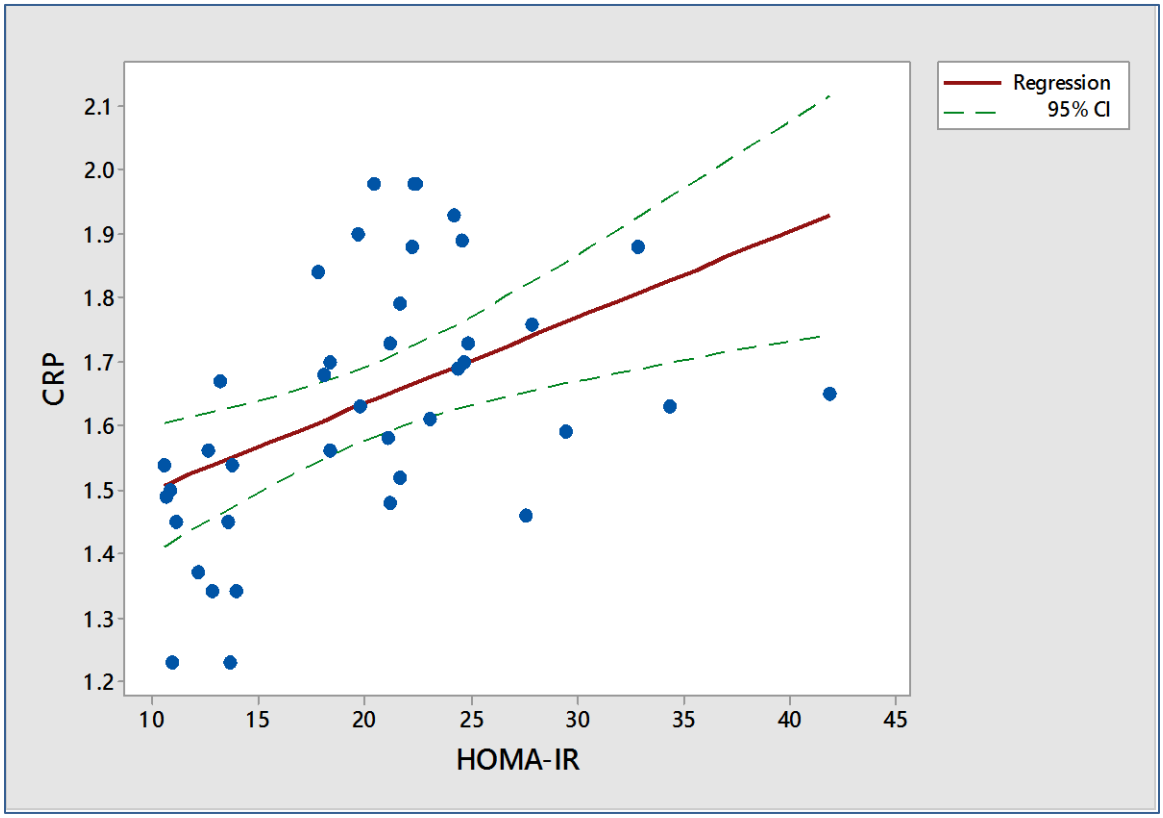
Variables of Study	**Obese diabetics n=40 Mean ± SD**	**Obese non Diabetics n=40 Mean ± SD**	**P value**
Age in Years	44 ± 7	40 ± 6	*0.0129
BMI in kg/m2	35 ± 5	33± 3	*0.0320

n = number of subjects
*significant

GLYCAEMIC PARAMETERS & CRP IN DIABETIC & NON DIABETIC GROUPS

Variables	Diabetics n=40 Mean ± SD	Non Diabetics n=40 Mean ± SD	P value
Blood Sugar Fasting mg/dl	164 ± 46	83 ± 8	*0.0001
Insulin IU/ml	37 ± 7	26 ± 6	*0.0001
HOMA –IR	19 ± 8	5 ± 1	*0.0001
CRP	2 ± 0.17	1 ± 0.20	*0.0001

n = number of subjects *significant



Correlation between C - reactive protein and HOMA -IR

DISCUSSION:

We conducted this study is to find correlation amongst obesity and Inflammation in obese type 2 diabetics and non diabetic subjects. Our chief conclusions support a positive linkage between BMI and CRP in obese diabetics which is in accordance with other researches done by [21,22 &23]

In the present study, obese diabetics had significantly higher BMI levels of plasma CRP as compared to obese controls. Obesity is frequently connected with resistance of insulin, increased production of pro inflammatory cytokines like TNF alpha & IL-6 and changes in distribution of body fat while persistent inflammation is well-thought-out to be a strong risk factor for evolving many diseases including diabetes. Badawi et al found overexpression of TNF-α in the overweight state, while they noted linkage of IL-6 more to the obese state which encourages the liver to produce and secrete C reactive protein, the clear feature of systemic inflammation [25-27]

Inflammation of chronic nature plays an important specific role in people with T2DM & simultaneous

obesity. Liver is thought to have a central role in inflammation as it drains FFA and flowing triacylglycerol endorsing cytokines IL-6 release by the adipose tissue that activates hepatocyte expression and release of CRP

Klisic et al evaluated levels of CRP and markers of metabolism amongst normal weight and overweight postmenopausal women in Montenegro [28] Likewise, Dayal et al recognized the anthropometric measurements role with CRP in Indian children. [29] Conversely some studies did not show any association between CRP, Obesity and diabetes mellitus [30]. Dissimilar stages of habitual actions and inhabitants of several ethnic backgrounds may be a valid reason of confusing the understanding of these conclusions. Certainly majority of T2DM patients are comparatively obese with higher BMI and insulin-resistance. Insulin resistance is believed to be induced by raised CRP levels. Surprisingly besides the absolute clear association of CRP & BMI, no relationship was noted between CRP & waist hip ratio which is an indicator of visceral obesity [31-3])

Hyperglycemia & Obesity are documented to encourage oxidative stress that leads to free radicals generation in diabetic subjects which may harm cell membrane and henceforth are associated with CRP elevation. We also proposed that the effects of obesity and hyperglycemia may lie beneath the elevation of CRP which indicates inflammatory processes. Our conclusions noted that levels of CRP in diabetics were 5.6 times more expected to be high than non diabetics which are in accordance with Furukawa et al. It thus looks like that elevated CRP levels in subjects with T2DM & obesity are the effect of concurrent impression of obesity & diabetes [34]

Comparable to these studies, Pravenec et al. found that in the liver of mice, transgenic expression of human CRP encourages inflammation and stimulates insulin resistance

We concluded presence of a link between serum CRP concentration and BMI. Obese diabetics subjects were found to have about double CRP levels than non-diabetics obese subjects. We found the most important factor which determines an increase in CRP concentration in obese T2D is presence of diabetes & excess body fat. Additional research on a large population sample size of type 2 diabetics is desirable to verify our results and examine the association between glycemic control and CRP as many studies have counter reports mentioning a positive significant correlation between elevated CRP levels & worse glycemic control. [35-7]

REFERENCES:

1. Deurenberg P, Deurenberg Yap M, Gurrici S, Obesity Reviews : an official journal of the international Association for the study of Obesity 2002;3 (3): 141-6
2. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr Obesity is associated with macrophage accumulation in adipose tissue. Journal of Clinical Investigation. 2003;112 (12):1796-1808. Doi 10.1172/JC1200319246
3. Qatanani, M., Lazar, M.A., Szwergold, N.R., Greaves, D. and Ahima, R. (2009). Macrophage-derived human resistin exacerbates adipose tissue inflammation and insulin resistance in mice. J. Clin. Invest., 119: 531-539.
4. Backes JM, Howard PA, Moriarty P. Role of C-reactive protein in cardiovascular disease. Ann Pharmacother. 2004;38:110–8.
5. American Diabetes Association. (2011). Diabetes Statistics- National Diabetes facts sheet Total prevalence of diabetes [online] Available at:http:// www. cdc.gov/ diabetes/ pubs/ factsheet11htm.
6. Votey, S.R. and Peters, A.L. (2010). Diabetes Mellitus, Type 2- A Review [online] Available at: URL: http://emedicine.medscape.com/article/766143-overview.
7. World Health Organization. Global report on diabetes. 1-84(2016)
8. Wild S, Roglic G, Green A, et al Global prevalence of diabetes. Diabetes care 2004;27 (5): 1047-1053
9. Obesity and inflammation: the linking mechanism and the complications Arch Med Sci. 2017 Jun; 13(4): 851–863.) 52.
10. Khardori, R. (2012). Type 2 Diabetes Mellitus. [online] Available at: http://emedicine.medscape.com/article/117853-overview.
11. Lumeng, C.N., Bodzin, J.L. and Salteil, A.R. (2007). Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J. Clin. Invest., 117: 175-184.
12. C-reactive Protein, Body Mass Index, and Diabetic Retinopathy.Investigative Ophthalmology & Visual Science September 2010, Vol.51, 4458-4463.
13. Charriere, G., Cousin, B., Arnaud, E., Andre, M., Bacou, F., Penicaud, L., and Casteilla, L. (2003). Preadipocyte conversion to macrophage. Evidence of plasticity. J. Bio. Chem., 278: 9850-9855.

14. Lehrke, M., Reilly, M.P., Millington, S.C., Iqbal, N., Rader, D.J. and Lazar, M.A.(2004). An inflammatory cascade leading to hyperresistinemia in humans. PLoS Med. Doi:10.1371/journal.pmed.0010045.
15. Hotamisligil, G.S. (2003). Inflammation, TNF α and Insulin Resistance. Am. J. Gastroenterol., **98**: 2751-2756.
16. Mohammed S. Ellulu, Ismail Patimah, Huzwah Khaza'ai, Asmah Rahmat, and Yehia Abed D Alessandris, C., Lauro, R., Presta, I. and Sesti, G. (2007). C-reactive protein induces phosphorylation of insulin receptor substrate-1 on serine 307 and Ser 612 in L6 myocytes, thereby impairing the insulin signalling pathway that promotes glucose transport. Diabetologia, 50: 840-849.
17. Pravenec, M., Kajiya, T., Zidec, V., Landa, V., Mlejnek, P., Simakova, M., Silhavy, J., Malinska, H., Oliyarnk, O., Kazdova, L., Fan, J., Wang, J. and Kurtz, T.W. (2011). Effects of Human C– Reactive Protein on pathogenesis of Features of Metabolic Syndrome. Hypertension, 57: 731-737.
18. Haffner, S.M., (2006). The metabolic syndrome: inflammation diabetes mellitus , and cardiovascular disease. Am. Cardiol. J., 97: 3-11
19. Ndumele, C.E., Pradhan, A.D. and Ridker, P.M. (2006). Interrelationships between inflammation, C-reactive protein, and insluin resistance. J. Cardiometab. Syndr., 1:190-196
20. Suganya Kanmani, Minji Kwon, Moon-Kyung Shin & Mi Kyung Kim Association of C-Reactive Protein with Risk of Developing Type 2 Diabetes Mellitus, and Role of Obesity and Hypertension: A Large Population-Based Korean Cohort Study Scientific Reports volume 9, Article number: 4573 (2019)
21. Baba MM, Balogun MO, Kolawole BA, Ikem RT, Arogundade FA, Adebayo RA. Relationship between C-reactive protein and body mass index in Nigerians with type II diabetes mellitus. Niger J Clin Med. 2012;4(3)
22. Unek IT, Bayraktar F, Solmaz D, et al. The levels of soluble CD40 ligand and C-reactive protein in normal weight, overweight and obese people. Clin Med Res. 2010;8(2):89–95
23. Badawi A, Klip A, Haddad P, et al. Type 2 diabetes mellitus and inflammation: prospects for biomarkers of risk and nutritional intervention. Diabetes Metab Syndr Obes. 2010;3:173–86.
24. Kahn SE, Zinman B, Haffner SM, et al. Obesity is a major determinant of the association of C reactive protein levels and the metabolic syndrome in type 2 diabetes. 2006; 55 (8): 2357-2364. Doi:10.2337/db06-0116
25. Anan F, Masaki T, Umeno Y et al, Correlations of high sensitivity C reactive protein and atherosclerosis in Japanese type 2 diabetes patients. European journal of Endocrinology 2007;157 (3): 311-317 doi10.1530/EJE-07-0388
26. Streja D, Cressey P, Rabkin SW. Associations between inflammatory markers, traditional risk factors & complications in patients with type 2 diabetes mellitus. Journal of diabetes & its complications 2003; 17 (3):120-127 doi: 10.1016/S1056-8727 (02) 00204-0
27. Klisic A, Vasiljevic N, Simic T, Djukic T, Maksimovic M, Matic M. Association between C-reactive protein, anthropometric and lipid parameters among healthy normal weight and overweight postmenopause women in Montenegro. Lab Med. 2014;45:12–6.
28. Dayal D, Jain H, Attri S, Bharti B, Bhalla A. Relationship of high sensitivity C-reactive protein levels to anthropometric and other metabolic parameters in Indian children with simple overweight and obesity. J Clin Diagn Res. 2014;8:PC05
29. Fukuchi, Y. et al. Immuno histochemical detection of oxidative stress biomarkers, Dityrosine & N(epsilon)-(hexanoyl)lysine & CRP in rabbit atherosclerotic lesions. J. Atheroscl. **15**, 185–192 (2008).
30. Jarva, H., Jokiranta, T. S., Hellwage, J., Zipfel, P. F. & Meri, S. Regulation of complement activation by C-reactive protein:Targeting the complement inhibitory activity of factor H by an interaction with short consensus repeat domains 7 and 8–11. J. Immunol. **163**, 3957–3962 (1999).
31. Aneta Fronczyk, Piotr Molęda, Krzysztof Safranow, Wiesław Piechota, and Lilianna MajkowskaIncreased Concentration of C-Reactive Protein in Obese Patients with Type 2 Diabetes Is Associated with Obesity and Presence of Diabetes but Not with Macrovascular and Microvascular Complications or Glycemic Control Inflammation. 2014; 37(2): 349–357.
32. Laurence Shen Lim; E. Shyong Tai; Paul Mitchell; Jie Jin Wang; Wan Ting Tay; Ecosse Lamoureux Tien Yin Wong
33. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004;114(12):1752–1761.
34. Trayhurn P, Wood IS, Adipokines: Inflammation and the pleiotropic role of white adipose tissue. British Journal of Nutrition. 2004; 92 (3): 347-355. doi 10.1079/BJN2004121330.

35. Sam S, Haffner S, Davidson MH, et al. Relation of abdominal fat depots to systemic markers of inflammation in type 2 diabetes. Diabetes care 2009;32 (5):932-937 doi10.2337/dc08-1856
36. Venugopal, S. K., Devaraj, S., Yuhanna, I., Shaul, P. & Jialal, I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. Circulation. **106**, 1439–1441 (2002