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STUDY OF ASSOCIATION BETWEEN EPICARDIAL FAT ADIPOCYTE SIZE, INSULIN RESISTANCE, ADIPOCYTOKINE LEVELS AND BODY COMPOSITION IN DIABETIC AND NON DIABETIC PATIENTS

Pathology

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ABSTRACT

Introduction : Diabetes mellitus is one of the most common metabolic diseases worldwide. Adipose tissue is not only a lipid storage unit, but it also functions as a paracrine and endocrine organ, secreting a number of adipocytokines such as leptin, adiponectin and tumor necrosis factor-α (TNF-α) etc. Abnormally accumulated visceral fat is a risk factor for insulin resistance. Epicardial adipose tissue (EAT) is a visceral adipose tissue that surrounds the myocardium and pericardium. It has recently been shown that enlargement of the adipocytes is an independent marker of insulin resistance. Larger adipocytes release higher amounts of proinflammatory mediators such as leptin and resistin, and lower amounts of adiponectin. Little is known about EAT cellularity. **Objective/Aim:** We aim to investigate EAT adipocyte size and its relationship with insulin resistance, circulating levels of adipocytokines, and body composition in Diabetic and Non Diabetic patients, in order to achieve a better insight into the physiology of epicardial adiposity. **Materials and Methods:** A one-year Single centre,hospital based comparative cross-sectional study conducted in 40 diabetic & 40 non-diabetic patients undergoing Cardiac surgery at CTVS Department of S.M.S.Hospital, Jaipur. Written explained informed consent were taken from all recruited patients. Fasting peripheral venous sample were collected for basic laboratory investigations. Radiological Assessment in form of MRI abdomen was done to determine abdominal subcutaneous and visceral fat percentage. Cardiac 2D echo was done for epicardial fat quantification. Epicardial adipose tissue was obtained by the operating surgeon in patients undergoing Cardiac surgery in vial containing Formalin. H &E stained slides were then examined under microscope. Pictures on 10x and 40x zoom were clicked and cell size measurements were taken. Statistical analyses were done using Medcalc 19.4 version for all statistical calculation **Results:** Most of the study population was elderly & Smoking & alcohol was observed more in Diabetics. W:H ratio in diabetic group cases was significantly higher as compared to non diabetic group cases showing that central obesity was more related with diabetics. Epicardial fat thickness was more in diabetics compared to non-diabetics…although Epicardial fat adipocyte size was found to be more in Non-diabetics. **Conclusion:** Significant difference with respect to W:H ratio shows role of central obesity in diabetics. Causal association of smoking and alcohol to diabetes may be considered. We concluded that epicardial fat thickness increases and adipocyte size decreases in diabetics which may be due to proliferation of smaller adipocytes, showing its association with insulin resistance, adipocytokine levels and body composition. As now a days routine health check up is recommended for all middle age and elderly persons, we feel(on the basis of this study) that EAT thickness must be measured while doing 2D-Echo and insulin resistance must be determined so that persons at risk of developing diabetes & potential CVD patients can be picked up at an early stage & their complications can be prevented.

KEYWORDS

epicardial fat, adipocyte size, insulin resistance, adipocytokines

INTRODUCTION:

Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide and is characterized as a metabolic disorder of carbohydrates, proteins and lipids. Adipose tissue is not only a lipid storage unit, but it also functions as a paracrine and endocrine organ, secreting a number of adipocytokines such as leptin, adiponectin and tumor necrosis factor-α (TNF-α), which have proinflammatory, atherogenic, or protective effects, and contribute to unfavorable metabolic and cardiovascular risk factors[1]. Abnormally accumulated visceral fat is a risk factor for insulin resistance, which can reduce insulin sensitivity, increase the expression and secretion of proinflammatory cytokines in adipose tissue and promote the development of DM and cardiovascular diseases[2]. Epicardial adipose tissue (EAT) is a visceral adipose tissue that surrounds the myocardium and pericardium. It is one of the visceral fat stores in the body.

Previous studies have suggested that measurements of EAT are a substitute for visceral fat[3]. EFT can secrete inflammatory factors, such as TNF-alpha, IL-6, adipocytokines, and leptin, via paracrine or endocrine activities[4] to locally regulate the myocardium and coronary artery function and regulate lipid and energy homeostasis in vivo. EAT has the ability to release and uptake free fatty acids and to affect low glucose utilization, which plays an important role in metabolic syndrome and coronary artery disease[5].

It has recently been shown that enlargement of the adipocytes is an independent marker of insulin resistance. Larger adipocytes release higher amounts of proinflammatory mediators such as leptin and resistin, and lower amounts of adiponectin[6].

Little is known about EAT cellularity. We aim to investigate EAT adipocyte size and its relationship with insulin resistance, circulating levels of adipocytokines, and body composition in Diabetic and Non Diabetic patients, in order to achieve a better insight into the physiology of epicardial adiposity.

MATERIALS AND METHODS

A one-year Single centre,hospital based comparative cross-sectional study conducted in 40 diabetic & 40 non-diabetic patients undergoing Cardiac surgery at CTVS Department of S.M.S.Hospital, Jaipur.

Study Population:

Inclusion Criteria:

1. Patients giving written informed consent for study.
2. Diabetic Cases: Patients with Impaired fasting Glucose, Impaired 75gm OGTT or frank Type 2 Diabetes Mellitus diagnosed as per ADA 2020 criteria.
3. Non diabetic Controls: Patients with normal FBS, PPBS, HbA1c or 75 gm OGTT.

Exclusion Criteria:

1. Patients denying consent.
2. Presence of Acute Infection or Malignancy

Study Procedure:

Written explained informed consent were taken from all recruited patients. Fasting peripheral venous sample were collected for basic laboratory investigations including: FBS, Fasting Insulin, HbA1c, Serum Creatinine, Uric acid, Lipid Profile, Leptin, Adiponectin, FFA, hsCRP, TNF alpha and IL-6. HOMA IR and HOMA beta were calculated using standard formulae. HOMA equations have been one of the tools widely used in research to estimate insulin resistance. The two equations (which use fasting blood levels) are as follows, with HOMA-IR used to assess insulin resistance and HOMA-β used to assess pancreatic beta–cell function:

- HOMA-IR = (insulin * glucose) / 22.5 for the glucose concentration in mmol/L
- HOMA-IR = (insulin * glucose) / 405 for glycemia in mg/dL. In both cases the insulin is in mU/L.

Radiological Assessment in form of MRI abdomen was done to

determine abdominal subcutaneous and visceral fat percentage. Cardiac 2D echo was done for epicardial fat quantification.

Epicardial adipose tissue was obtained by the operating surgeon in patients undergoing Cardiac surgery in two separate vials containing All Protect Solution and Formalin respectively.

The EAT samples were fixed in 10% formalin for histopathological examination. Then paraffin embedded blocks were made in the usual manner and thin sections of 3-5 microns were cut by using a microtome. Sections were stained by Haematoxylin and Eosin. Slides were then examined under microscope. Pictures on 10x and 40x zoom were clicked using Nikon digital camera fitted on the Microscope. After that the pictures were opened in Photoshop CC tools and cell size measurements were taken.

Subjects underwent detailed clinical evaluation including clinical history, physical examination including general physical and systemic examination, examination for acanthosis nigricans and anthropometric measurements [height, weight, body mass index [BMI], waist (WC) and hip (HC) circumferences, waist to hip circumference ratio (WHR)].

Data Management And Statistical Analysis

Statistical analyses were done using Medcalc 19.4 version for all statistical calculation. The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analysed by using chi square test and the difference in means among the groups was analyzed using the student T Test.Correlation between quantitative outcomes was assessed using Pearson correlation coefficient. 5% probability level was considered as statistically significant i.e., $p<0.05$.

OBSERVATIONS & RESULTS

Diabetic and non diabetic patients undergoing cardiac surgery were comparable as per age & mostly from elder age group. Mean ± SD value for Diabetic and Non Diabetic respectively were 58.97±8.70 and 60.26±9.07 and male preponderance was observed in this study.

There was a significant difference among the groups for smoking and alcohol whereas for tobacco, it was not there. For smoking and alcohol, diabetic group cases were more as compared to non diabetic group cases. Significant difference among the groups was found only for W:H ratio and rest for all other such as BMI, Waist & Hip Circumference, no significant difference was found. Mean ± SD value for W:H ratio in diabetic group cases was significantly higher as compared to non diabetic group cases (P=0.019S). This means that central obesity is more related with this study group.

Table/Fig. 1: Comparison of Baseline characteristics

		Diabetic		Non Diabetic		p-values
		Number	Percentage (%)	Number	Percentage (%)	
	Total	**40**	100	**40**	100	
Age	≤40	1	2.5	1	2.5	1.000NS
	41-50	7	17.5	7	17.5	
	51-60	12	30	10	25	
	>60	20	50	22	55	
	Mean ± SD	**58.97±8.70**		**60.26±9.07**		0.522NS
Gender	Female	8	20	12	30	0.181NS
	Male	32	80	28	70	
Personal Habbits	Smoking	23	62.16	9	20.93	0.003S
	Tobacco	12	32.43	16	37.21	0.482NS
	Alcohol	11	29.73	3	6.98	0.039S
Anthropometery	BMI(kg/m2)	24.69	3.76	24.57	4.09	0.891NS
	Waist circumference (cm)	90.96	11.98	88.56	9.16	0.313NS
	Hip circumference (cm)	93.88	11.97	94.93	5.02	0.601NS
	W:H	0.97	0.06	0.93	0.08	0.019S

There was a significant difference between the groups for fasting blood sugar, HbA1c & insulin resistance, but for Insulin, it was not the case.Fasting Blood sugar and HbA1C were significantly higher in Diabetic as compared to non diabetic group (P<0.001S). For HOMA-B, Mean ± SD value was higher in non diabetic as compared to diabetic group cases whereas for HOMA IR and Fasting Glucose, it was vice versa.(P<0.001S).

Table/Fig. 2: Comparison of insulin resistance between diabetic & non diabetic

Gr	Diabetic		Non Diabetic		P Value LS
	Mean	SD	Mean	SD	
Insulin (mu/L)	8.2	1.74	7.65	1.27	0.211NS
Fasting blood sugar (mg/dL)	180.77	60.93	104.72	22.29	<0.001S
HbA1c (%)	8.34	2.37	5.53	0.49	<0.001S
HOMA- B	31.75	16.61	92.76	52.31	<0.001S
HOMA IR	3.77	1.39	1.94	0.4	<0.001S

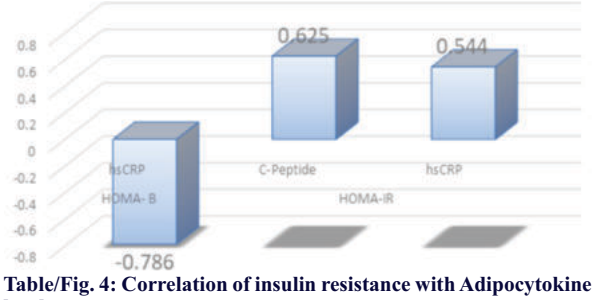
No significant difference was found among the groups in Adipocytokine level (C-Peptide hsCRP,, Adiponectin , Leptin , IL-6 and TNF-α).

No significant difference was found among the groups on comparison of abdominal fat(visceral as well as subcutaneous fat) as measured by MRI.

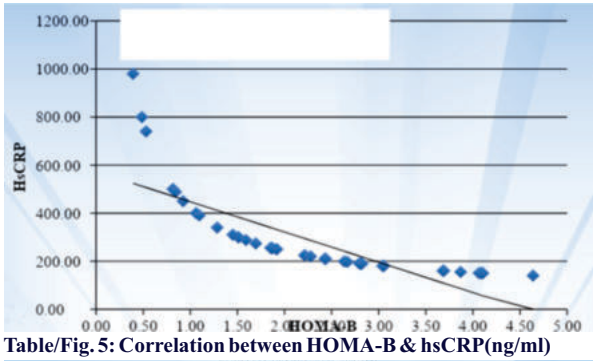
Table/Fig. 3: Correlation of insulin resistance with Adipocytokine levels

Correlations							
		C-Peptide (ng/ml)	hsCRP (ng/ml)	Adiponectin (µg/ml)	Leptin (ng/ml)	IL-6 (pg/ml)	TNF-α (pg/ml)
HOMA-B	Pearson Correlation	0.026	-.786**	0.052	0.02	0.098	0.116
	Sig. (2-tailed)	.863NS	<0.001S	.728NS	.892NS	.512NS	.439NS
HOMA-IR	Pearson Correlation	.625**	.544**	-0.028	0.014	-0.25	-0.285
	Sig. (2-tailed)	<0.001S	<0.001S	.852NS	.926NS	.091NS	.052NS

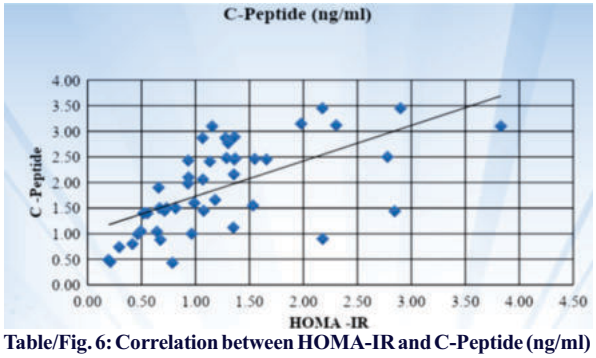
The above table depicts the Correlation between Insulin Resistance (HOMA –B) and Adipocytokine levels in cases where we have found that there was a significant difference among the group only for hsCRP (r=-.786** good correlation, P<0.001S) .There was no significant difference found among the groups for Adiponectin, Leptin, IL-6 and TNF- α whereas it was vice versa for C-Peptide and hsCRP while correlating with HOMA-IR.



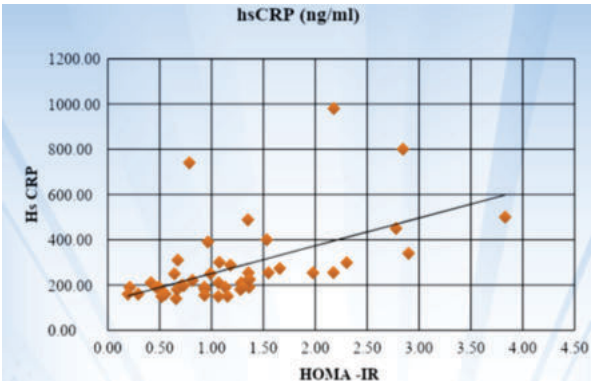
Table/Fig. 4: Correlation of insulin resistance with Adipocytokine levels



Table/Fig. 5: Correlation between HOMA-B & hsCRP(ng/ml)



Table/Fig. 6: Correlation between HOMA-IR and C-Peptide (ng/ml)

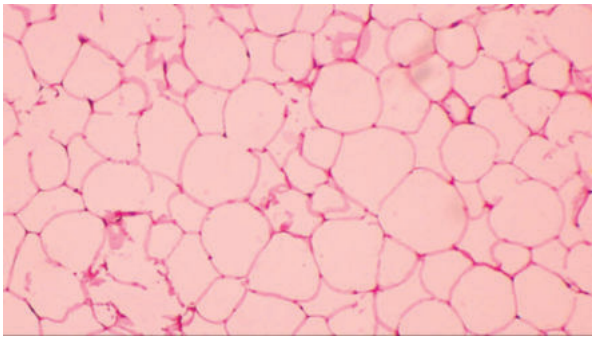


Table/Fig. 7: Correlation between HOMA-IR and hsCRP (ng/ml)

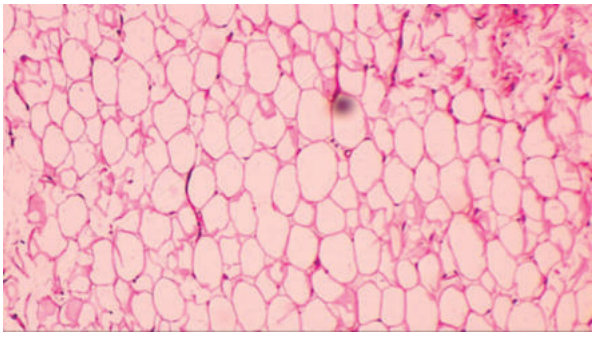
Table/Fig. 8: Comparison of Epicardial Fat adipocyte size in Diabetic and Non Diabetic

Group	Diabetic		Non-Diabetic		P Value LS
	Mean (μm^2)	SD	Mean (μm^2)	SD	
AT 10X	20520.48	7378.94	30141.50	19308.96	0.118NS

The above table depicts that there was no significant difference among the groups although the size of the **adipocytes were slightly more in non diabetic group as compared to diabetics groups.**



NON-DIABETIC



DIABETIC

Table/Fig. 9: Photo Micrograph Of Epicardial Adipose Tissue (For Measurement Of Cell Size)10x

DISCUSSION:

Epicardial adipose tissue (EAT) in the LAVG was significantly associated with type 2 diabetes mellitus and obesity independently.[7] It is defined as the adipose tissue between the myocardium and the visceral layer of the pericardium [8,9]. Epicardial fat covers 80% of the heart's surface and constitutes 20% of the total heart weight. EAT is present along the coronary arteries and over the right ventricle, especially along the acute margin and atrioventricular and interventricular grooves (IVGs) [10]. Therefore to find out the relation between these this study was conducted on 40 Diabetic and 40 Non Diabetic cases.

In the present study, Diabetics undergoing cardiac surgery were younger compared to non-diabetics , similar results were obtained in study conducted by Aurora del , et al. (2016)[11] where it was observed that Diabetic patients showed a tendency to be younger as compared to Non Diabetics.

Male preponderance was observed in this study. Similar findings were observed in Aurora del, et al. (2016),[11] the male sex around the 6th decade of life was predominant, which is consistent with widely reported data; for example, in the RENASCA study (Borrayo S, et al. 2010)[12] conducted in Mexico in 2010, which included 2,389 patients with ischemic heart disease admitted to tertiary care hospitals of the National Institute of Social Security (IMSS – InstitutoNacional del Seguro Social), 71% of registered patients were males.

Smoking was significantly higher in proportion in diabetic as compared to non-Diabetic group.(P=0.003S). Similar observation were found in the study conducted by Aurora del, et al. (2016)[11] that smoking was observed in more than half the population.

Central obesity was more related with this study group because W:H ratio was more strongly associated with diabetes than BMI [13].This is in line with Aurora del, et al. (2016)[11] who also observed that obesity was found in more than half the population.

Levy BI, et al. (2008)[14] found that up to 41% of diabetic patients had combined hypercholesterolemia and hypertension, exponentially increasing cardiovascular risk.

Raised TG levels, often found in T2DM, are assumed to be associated with systemic inflammation[15]. *Grunfeld C, et al* also believed it to be independent risk contributors to coronary artery disease (CAD), a major vascular complication associated with the disease.[15]

In contrast to above mentioned studies, our study shows no significant difference in lipid profiles of diabetics and non diabetics. It may be due to, in our study setting, all patients were on medication and this study was conducted in government set up which is free set up, where most of footfall belonged to lower SES population who were poor, undernourished.

The Homeostasis Model Assessment of IR (HOMA-IR) has proved to be a robust tool for the surrogate assessment of IR.[16] However, there is great variability in the threshold HOMA-IR levels to define IR[17]. In our study, we found that for HOMA-B, Mean ± SD value for non diabetic was higher as compared to diabetic group cases whereas for HOMA IR and Fasting Glucose, it was vice versa (P<0.001S). This is in line with the research study, Prakash D, et al. (2008)[18], Cherneva ZV, et al. (2011)[19] elevated plasma glucose has been shown to entail a somber prognosis with regard to normoglycemia in AMI. Aurora del, et al. (2016)[11] observed that Glucose (mg/dl) 100.0 (100.2 ± 121.1) were in non diabetics as compared to diabetic cases 173.5 (152.2 ± 224.7) . Amauchi K, et al.[20] found that HOMA B was significantly higher in non diabetics as compared to diabetics (104.9 vs 95.6) and its vice versa was observed in HOMA IR (1.95 vs 5.212) P<0.001S.

Mean ± SD value for epicardial fat adipocyte size of non diabetic and diabetic respectively were 30141.50±19308.96 and 20520.48±7378.94 (no significant difference was observed among the group), this agreed with Waldeker, et al. (2009)[21] who found no difference in adipocyte size between diabetic and non-diabetic specimens, Wang YN, et al. (2011)[22] observed that no significant difference was observed in the interdigitation index or adipocyte size but is in contrast with Buschmann et al.[23], who reported a 30% decrease in adipocyte mean area and a 16% decrease in mean adipocyte diameter in diabetic plantar soft tissue. Although mean adipocyte cell minimum diameters were not found to be statistically different for diabetic compared to non-diabetic tissue , the mean values tended to be larger in the diabetic tissue (area, 2160 ± 451 μm^2 versus 1812 ± 492 μm^2; min. diameter, 45 ± 4.9 µm versus 40.7 ± 5.6 µm)

Previous studies have correlated epicardial adipocyte size with inflammatory cytokine release and insulin resistance.[24,25] Similarly, the EAT transcriptome has been found to be altered in patients with coronary artery disease, resulting in differential expression of inflammatory and apoptotic genes, which might alter the size of epicardial adipocytes.[26,27]

CONCLUSION

We concluded that

- Mean adipocyte cell minimum diameters were not found to be statistically different for diabetic compared to non-diabetic patients undergoing cardiac surgery. Although EAT thickness was found to be more in diabetic than non-diabetic.

- In 2D Echo, apex epicardial fat was observed higher in study population.
- Significant difference with respect to W:H ratio which shows role of central obesity in study group.
- Smoking and alcohol showed significant association with diabetic patient .
- Significant correlation was observed with higher circulating inflammatory C-Peptide (ng/ml) and hsCRP (ng/ml) to insulin resistance.
- In our study we concluded that insulin resistance of adipocytes may be considered as one of the factors mediating this relationship, also central obesity which is also significant predictor of DM and epicardial adipose tissue (EAT) thickness are also recognized as one of the factors in the development of cardiometabolic diseases .
- Therefore we can conclude that epicardial fat thickness increases and adipocyte size decreases(although not stastically significant) in diabetics which may be due to proliferation of smaller adipocytes, showing its association with insulin resistance, adipocytokine levels and body composition.

Limitations, Strength & Recommendation

Limitations:

Following limitations were observed in our study.

- Most of the subjects were from middle to poor socio-economic status resulting in not reflecting obesity and related parameters correctly.
- Most of the patients in diabetic group were on medication like statins and anti-diabetic (including insulin) for long time resulting in change in parameters under study.

Strength

- All investigations were non invasive and can be done with pre-operative routine investigation using same blood samples.
- Alongwith routine 2D Echo epicardial fat thickness can be measured with no extra efforts and discomfort to patients.
- During CABG small amount of epicardial fat tissue can be taken without any harmful effects to the patients.

Recommendation

- Multi centric bigger studies are required so that all socio-economic profile is represented equally in study population, because variation in obesity is observed between different socio-economic groups resulting in variation in related parameters.
- As now a days routine health check up is recommended for all middle age and elderly persons, we feel(on the basis of this study) that EAT thickness must be measured while doing 2D-Echo and insulin resistance must be determined so that persons at risk of developing diabetes & potential CVD patients can be picked up at an early stage & their complications can be prevented.

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