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Association of visceral fat with cardiopulmonary fitness, oxidative stress and inflammatory markers in asymptomatic individuals with and without family history of type 2 diabetes mellitus

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***Abstract*---**Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with derangement of carbohydrate, fat, and protein metabolism due to absolute or relative deficiency of insulin secretion and action, or both. DM, especially type-2 DM, is a serious general medical issue which has arrived at scourge extents because of the quickly expanding paces of this ailment around the world. Target organ confusions, auxiliary to diabetes, are one of the most significant restorative worries of right now. The main findings of our research were no significant differences in baseline characteristics like age and height of both groups. Weight, BMI and waist hip ratio was significantly high in cases. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and rate pressure product were significantly high in Cases individuals; however, no significant difference was noticed in pulse pressure (PP). Significantly higher body fat and visceral fat %, lower levels of cardio respiratory fitness assess by cooper 12min run test and significantly higher levels of fasting blood sugar (FBS) was observed in cases. The oxidative stress assessed by total antioxidant status (TAOS) was significantly less and

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malondialdehyde (MDA) was significantly high in cases when compared to age gender matched controls. Inflammatory markers TNF alpha, IL6 and hsCRP were significantly high in cases in comparison to controls.

***Keywords*---**Hyperglycemia, Diabetes Mellitus, Asymptomatic, Polyphagia.

Introduction

The constellation of abnormalities caused by insulin deficiency is called Diabetes mellitus (DM). Greek and Roman physicians used the term to refer to conditions in which the cardinal finding was a large urine volume, and two types were distinguished. “Diabetes mellitus” in which the urine tasted sweet, and “Diabetes insipidus” in which the urine had little taste. Diabetes mellitus is characterized by polyuria, polydipsia, and weight loss in spite of polyphagia, hyperglycemia, glycosuria, ketosis, acidosis and coma.

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with derangement of carbohydrate, fat, and protein metabolism due to absolute or relative deficiency of insulin secretion and action, or both. DM, especially type-2 DM, is a serious general medical issue which has arrived at scourge extents because of the quickly expanding paces of this ailment around the world. Target organ confusions, auxiliary to diabetes, are one of the most significant restorative worries of right now. According to a recent World Health Organization (WHO) report, India, with 32 million diabetic individuals, currently has the highest incidence of diabetes worldwide; this may be increased to 80 million by the year 2030 [1]

Inflammation is a defensive mechanism of the body. Be that as it may, in interminable illnesses like, diabetes mellitus, hypertension, asthma and so forth., this defensive system turns into a significant component for movement of sickness. In Type 2 diabetes mellitus the diminishing β cell mass is likewise connected with glucose harmfulness interceded through IL-1β incited apoptosis. There are numerous examinations accentuating the nearness and significance of the fiery part in the pathogenesis of Diabetes mellitus. A very important role is played by adipose tissue, which releases various pro-inflammatory cytokines, such as, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), C Reactive Protein (hs CRP) [2,3,4]. Hyperglycemia produces reactive oxygen species (ROS), which in turn cause damage to the cells in many ways. Damage to the cells ultimately results in secondary complications in diabetes mellitus[5]. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications [6]. A well-established correlation exists between the development of macro and micro vascular disease in diabetes mellitus [7]. In diabetics, the hyperglycemic status was the primary cause for including oxidative stress. Further increase in oxidative stress is due to autoxidation of glucose and advanced glycation end products. Advanced glycation end product is a varied compound expected to play a major role in diabetes and its consequences [8]. Reports suggest oxidative stress is predominantly involved

in the pathophysiology of diabetes [9,10], and in the increase of effects of DM. Also, the beta cell dysfunction and IR that occur much earlier before the onset of diabetes are related to oxidative stress [11]

Aim & objectives

Aim: To examine the association of visceral fat with cardiopulmonary fitness, oxidative stress and inflammatory markers in asymptomatic individuals with and without family history of type 2 diabetes mellitus.

Objectives:

- To estimate the visceral fat, cardiopulmonary fitness, in asymptomatic individuals with and without family history of type 2 diabetes mellitus.
- To estimate the oxidative stress and inflammation markers in asymptomatic individuals with and without family history of type 2 diabetes mellitus.

Materials and Methods

After getting clearance from institutional ethics committee, all the subjects gave written and informed consent.

Type of study: Cross sectional study
Sampling technique: Random sampling
Sample size formula:

$$n = \frac{(Z_{1-\beta} + Z_{1-\alpha/2})^2}{(r^2 / 1-r^2)}$$

r = corrélation coefficient
Z1-α/2 = Desired confidence level
1- β = power

Group 1: FDRDM – 50,
Group 2: Controls: 50.

Sample size: Sample size was computed basing on expecting an association of levels of visceral fat composition with oxidative stress, inflammation may be 0.56.For testing that it could be significantly varies from 0 at alpha-error of 0.05 and power 90%, with two sided test, we needed to conduct a study thirty seven subjects in each of the group. After interim analysis, sample size was adjusted to 50 in each group.
No of groups: 2
Sample size: 100

Subjects: Apparently healthy cases in the age group of 18 - 30 y who accompanies with DM patients in F.H. Medical college and Hospital, Agra, India and students were considered for study as cases (n = 50). Individuals who are using any medicines for any health condition to restrict in performing sub-maximal exercise and individuals who are practicing regular physical activity, yoga, and/other bio-feedback were excluded from this study were not included in thi study. Candidate who showed willingness to enroll in the study were included.

Age and gender matched apparently healthy individuals with no family history of diabetes were recruited for control group (n = 50). Participants were requested to have adequate sleep one day before recording and to refrain from caffeinated beverages, exercise, alcohol and nicotine 24 h prior to recording. Individuals were asked to report to the Department of Physiology in the morning after overnight fasting (149). The fasting venous blood sample (5 mL) was drawn in sodium fluoride tubes from median cubital vein for biochemical analysis of lipid profile, inflammatory markers and oxidative stress markers, as soon as they reported to lab. They were then oriented to research lab and explained about the procedures that will be done on subsequent day.

Results

Table 1: Demographic profile of without family history of type 2 diabetes mellitus (controls) and with family history of type 2 diabetes mellitus subjects (cases)

Parameters	Age Distribution	Controls without family history of type 2 diabetes			Cases with family history of type 2 diabetes			P value
		N	Mean	Std. Deviation	N	Mean	Std. Deviation	
Height (cm)	18-21 Years	38	166.87	8.061	29	165.69	10.410	0.334
	22-25 Years	12	167.75	8.281	21	161.67	9.329	0.662
Weight (kg)	18-21 Years	38	58.24	9.431	29	69.10	13.230	0.030
	22-25 Years	12	57.75	11.145	21	64.38	6.320	0.295
BMI (kg/m^2)	18-21 Years	38	20.93	2.37	29	25.67	4.90	0.005
	22-25 Years	12	20.51	2.38	21	25.37	2.19	0.841
WHR	18-21 Years	38	0.82	0.06	29	0.84	0.05	0.098
	22-25 Years	12	0.80	0.10	21	0.85	0.04	0.062

Table 2. Cardiovascular parameters of individuals based on age distribution among the study population

Parameters	Age Distribution	Controls without family history of type 2 diabetes			Cases with family history of type 2 diabetes			P value
		N	Mean	Std. Deviation	N	Mean	Std. Deviation	
HR (bpm)	18-21 Years	38	80.34	3.34	29	88.45	3.92	0.507
	22-25 Years	12	77.83	2.86	21	86.81	2.94	0.626
SBP (mmHg)	18-21 Years	38	114.26	4.58	29	124.07	4.36	0.073
	22-25 Years	12	111.00	2.63	21	124.38	3.98	0.015

DBP (mmHg)	18-21 Years	38	75.74	3.19	29	84.21	3.56	0.316
	22-25 Years	12	73.50	3.63	21	84.76	3.71	0.591
PP (mmHg)	18-21 Years	38	38.53	3.50	29	39.86	6.23	0.116
	22-25 Years	12	37.50	4.91	21	39.62	5.24	0.793
MAP (mmHg)	18-21 Years	38	88.58	3.33	29	97.49	2.48	0.016
	22-25 Years	12	85.99	2.39	21	97.97	2.89	0.207
RPP	18-21 Years	38	9175.80	447.12	29	10980.0	724.15	0.005
	22-25 Years	12	8636.30	286.95	21	10801.0	583.38	0.021

Table 3: Body fat distribution, cardio respiratory fitness and blood glucose levels based on age distribution among the study population

Parameters	Age Distribution	Controls without family history of type 2 diabetes			Cases with family history of type 2 diabetes			P value
		N	Mean	Std. Deviation	N	Mean	Std. Deviation	
Body fat (%)	18-21 Years	38	24.10	1.66	29	26.91	2.25	0.210
	22-25 Years	12	24.32	1.66	21	24.49	2.62	0.005
Visceral fat (%)	18-21 Years	38	6.42	0.56	29	7.45	2.23	0.000
	22-25 Years	12	6.34	0.65	21	9.33	2.75	0.004
12 min run (meters)	18-21 Years	38	2767.0	65.39	29	2313.7	179.32	0.007
	22-25 Years	12	2734.2	119.83	21	2289.4	292.38	0.016
FBS (mg/dl)	18-21 Years	38	84.29	4.37	29	88.03	4.95	0.534
	22-25 Years	12	83.91	4.74	21	87.29	4.37	0.746

Table 4: Oxidative stress markers levels based on age distribution among the study population

Parameters	Age Distribution	Controls without family history of type 2 diabetes			Cases with family history of type 2 diabetes			P value
		N	Mean	Std. Deviation	N	Mean	Std. Deviation	
TAOS (mM)	18-21 Years	38	1.45	0.34	29	0.71	0.46	0.061
	22-25 Years	12	1.37	0.47	21	0.45	0.14	0.003
MDA (mM)	18-21 Years	38	6.14	.89	29	11.05	9.26	0.000
	22-25 Years	12	5.74	1.19	21	13.05	9.34	0.000

Table 5: Inflammatory markers levels based on age distribution among the study population

Parameters	Age Distribution	Controls without family history of type 2 diabetes			Cases with family history of type 2 diabetes			P value
		N	Mean	Std. Deviation	N	Mean	Std. Deviation	
TNF alpha (pg/ml)	18-21 Years	38	120.00	50.66	29	275.00	74.31	0.001
	22-25 Years	12	145.50	52.89	21	296.63	80.41	0.075
IL 6 (pg/ml)	18-21 Years	38	4.96	1.01	29	13.28	1.11	0.538
	22-25 Years	12	4.51	1.08	21	13.83	1.44	0.558
hsCRP (ng/ml)	18-21 Years	38	3051.20	528.29	29	9377.20	2105.32	0.000
	22-25 Years	12	2834.40	462.68	21	9025.00	3048.21	0.000

Table 6: Lipid profile based on age distribution among the study population

Parameters	Age Distribution	Controls without family history of type 2 diabetes			Cases with family history of type 2 diabetes			P value
		N	Mean	Std. Deviation	N	Mean	Std. Deviation	
TC (mg/dl)	18-21 Years	38	163.26	23.81	29	209.34	14.85	0.001
	22-25 Years	12	177.42	27.98	21	211.29	16.61	0.010
HDL (mg/dl)	18-21 Years	38	40.87	6.20	29	39.35	5.56	0.167
	22-25 Years	12	43.97	6.93	21	40.87	6.22	0.173
TGL (mg/dl)	18-21 Years	38	123.44	18.87	29	144.07	9.96	0.000
	22-25 Years	12	130.08	20.03	21	147.48	16.70	0.147
LDL (mg/dl)	18-21 Years	38	97.71	16.87	29	141.60	16.24	0.650
	22-25 Years	12	107.43	19.54	21	140.92	18.80	0.841
VLDL (mg/dl	18-21 Years	38	24.68	3.77	29	28.74	2.02	0.000
	22-25 Years	12	26.02	4.01	21	29.49	3.34	0.147

Discussion

In the present study, statistically not significant difference in mean and standard deviation of heart rate in 18-21 years in control group (80.34 $\pm$ 3.34 bpm) and case group (88.45 $\pm$ 3.92 bpm) (p=0.57), besides change in HR in 22-25 years in

18-21 years in control group (77.83 ± 2.86 bpm) then case group (86.81 ± 2.94 bpm) (p=0.62) (Table 2). The interesting finding of another study was significantly increased heart rate with family history of type 2 diabetes in Koizumi K et.al. [12] Alike a study also conducted by Nielsen et al there is a change in heart rate between case and control group. [16] Conflicting, a study also reported by Eckberg DL et al there is no change in heart rate between case and control group. [13] Contrary, a study also reported by Hedman AE et al there is no change is heart rate between case and control group. Increase in heart rate due to attributed to dominant of sympathetic activity over parasympathetic activity in case group. [14] In our study presume that the subjects with family history of type 2 diabetes has more HR compare with control group.

Our findings about increase in heart rate in case group is also supported by Hainsworth R et.al. They proposed that, an exaggerated cardiovascular reactivity to stressors is known to be a risk factor for cardiovascular diseases whereas reduced reactivity is an indicator of fitness. Therefore, a reduction in exercise-induced stress on cardio-vascular system by walking exercise has physiological significance as well as clinical applications. [15]

In our present study, in 18-21 years in case group after walking test of SBP (124.07 ± 4.36 mmHg) and DBP (84.21 ± 3.56 mmHg) are significantly increased in case group than control group of SBP (114.26 ± 4.58 mmHg) and DBP (75.74 ± 3.19 mmHg), additionally in 22-25 years in case group of SBP (124.38 ± 3.98 mmHg) and DBP (84.76 ± 3.71 mmHg) are significantly increased in case group than control group of SBP (111.00 ± 2.63 mmHg) and DBP (73.50 ± 3.63 mmHg) (Table 2). In our finding is suggestive of efficacy of walking exercise in modulating the cardiovascular response to exercise. Our results showing that increase in SBP and DBP in case group are similar to the results of Bhatt DL, et.al. [16] Identical study also reported by Azizi M et al there is change of SBP and DBP between case and control group. [17] Contrary, a study also reported by Bisognano JD et al there is no change is SBP and DBP between case and control group. [18] Opposing, a study also reported by Booth et al there is no change of SBP and DBP between case and control group. [19] This positive response might be indicating that more stress is produced on heart muscle during exercise in case group.

Moreover, pulse pressure (PP) in 18-21 years in case group (39.86 ± 6.23 mmHg) and control group (38.53 ±3.50 mmHg) was statistically not significant difference (p=0.11), similarly PP in 22-25 years in case group (39.62 ± 5.24 mmHg) and control group (37.50 ±4.91 mmHg) was statistically not significant difference (p=0.79). The mean arterial pressure (MAP) was statistically significant difference in 18-21 years in case (97.49 ± 2.48 mmHg) and control group (88.58 ± 3.33 mmHg) (p=0.016), alike in 22-25 years of MAP was statistically significant difference in 18-21 years in case (97.97 ± 2.89 mmHg) and control group (85.99 ± 2.39 mmHg) (p=0.207). On the other hand, Rate Pressure Product (RPP) also statistically significant difference between both the case (10980.0 ± 724.15) and control group (9175.80 ± 447.12) (p=0.021). A study by Heusser K et.al reported significant change in MAP and RPP in case group compared to control group. [20] Contrary, a study also reported by Robertson D et al there is no change is MAP and RPP between case and control group. [21] Opposing, a study also reported by

Norel X et al there is no change of MAP and RPP between case and control group. [22]

Body fat in 18-21 years in *Case Group* showed an increase in Mean percentage 26.91 ± 2.25 then control group 24.10 ± 1.66 (p=0.21), comparable Body fat in 22-25 years in *Case Group* showed an increase in Mean percentage 24.49 ± 2.62 then control group 24.32 ± 1.66. It shows that body fat increased in case group was 1.39 %. Ainsworth BE et al., have also observed similar results among a study population. [23] Most obese individuals, despite being insulin resistant, do not develop hyperglycaemia. Alike, a study also reported by Alahmadi MA et al there is change in body fat between case and control group. [24] Differing, a study also reported by Andersen RE et al there is no change in body fat between case and control group. [25] Contrary, a study also reported by Bahr R et al there is no change in body fat between case and control group. [26] Pancreatic β-cells of the islet of Langerhans release adequate amounts of insulin that are sufficient to overcome insulin level reductions under normal circumstances, thus maintaining normal glucose tolerance.

The **FBS** in between 18-21 years in *Case Group* showed an increase in Mean levels 88.03 ± 4.95 mg/dl then control group 84.29 ± 4.37 mg /dl (p=0.53), likewise **FBS** in between 22-25 years in *Case Group* showed an increase in Mean levels 87.29 ± 4.37 mg/dl then control group 83.91 ± 4.74 mg /dl (p=74). It reflects that 18-21 years of Mean increase of blood glucose was 3.74 mg/dl in case group then Control Group in our study. According to King P et al stated that increase in blood glucose level in case control study. [27] Similarly, a study also reported by Koyama Y et al there is change in FBG between case and control group. [28] Differing, a study also reported by Arciero PJ et al there is no change of FBG between case and control group. [29] Contrary, a study also reported by Boden G et al there is no change is Fasting blood glucose between case and control group. [30]

Data strongly support a genetic predisposition to β-cell failure. A genetic subtype of the disease characterized by diagnosis at <25 years of age, β-cell dysfunction, an autosomal dominant mode of inheritance, and heterozygous mutations in β-cell transcription factors has been identified as a common cause of early-onset type 2 diabetes. However, in most patients in clinical practice, it is impossible to identify a genetic abnormality clinically and environmental factors predominate. [31]

TAOS while comparing between control group (without family history of type 2 diabetes) and case group (with family history of type 2 diabetes), in our study found that in mean and standard deviation of TAOS in 18- 21 years in control group (1.45 ± 0 .34 mM) and case group (0.71 ± 0.46 mM) was statistically not significant difference between both groups (p=0.061), meanwhile TAOS in 22- 25 years in control group (1.37 ± 0 .47 mM) and case group (0.45 ± 0.14 mM) was statistically significant difference between both groups (p=0.003). MDA in 18-21 years in *Case Group* showed an increase in Mean 11.05 ± 9.26 mM then control group 6.14 ± 0.89m M (p<0.0001), MDA in 22-25 years in *Case Group* showed an increase in Mean 13.05 ± 9.34 mM then control group 5.74 ± 1.19m M. Similar results were obtained by Kashyap MK et al in-case group then control group. [32]

Alike, a study also reported by Banarjee S et al there is change TAOS and MDA between case and control group. [33] Conflicting, a study also reported by Kunwar A et al there is no change in TAOS and MDA between case and control group. [32] Contrary, a study also reported by Yoshikawa T et al there is no change in TAOS and MDA between case and control group. [34]

Conclusion

From the present study results it can be concluded that in our present study, case group (with family history of type 2 diabetes) and control group (without family history of type 2 diabetes) as per study protocol. The parameters of Cardiovascular system (HR, SBP, DBP, PP, MAP, RPP), FBS, visceral fat, Inflammatory markers (TNF alpha, IL6, hsCRP) and Lipid Profile (TC, HDL, TGL, LDL, VLDL).

The molecular genetic definition of T2DM pathophysiology will certainly satisfy our intellectual curiosity about this common disease, but will it impact health care. Our knowledge to predict T2DM is currently limited. Pharmacological intervention rather than prevention remains the primary approach to this disease. These investigations achieved a notable four–fold increased risk in with family history of type 2 diabetes This study is a landmark in combining individually weak genetic risk factors with traditional risk factors to improve the prediction of future T2DM. Although the combination of genetic risk factors in this model has been challenged, the methods of Lyssenko and colleagues model was in which multiple small genetic risk factors can be combined to predict risk. The utility of genetic approaches will depend on a holistic understanding of the interactions of among genetic variants, and between genetic variants and the environmental, lifestyle factors and treatments.

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