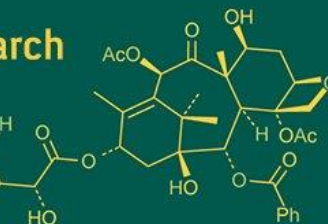
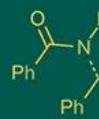


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Association of obesity with cardiorespiratory fitness and oxidative stress markers in apparently healthy adults with and without family history of type 2 diabetes mellitus

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Abstract

Introduction: Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders worldwide and its development is primarily caused by a combination of two main factors: defective insulin secretion by pancreatic β -cells and the inability of insulin-sensitive tissues to respond to insulin. Obesity and T2DM have emerged as new drivers of cardiovascular disease (CVD) risk. Increased oxidative stress is a well-known contributor to the onset and progression of diabetes, as well as its complications.

Materials and Methods: This is a cross-sectional observational study conducted at the Department of Biochemistry, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, from April 2018 to March 2019. Apparently healthy first-degree relatives of T2DM patients aged 18-60 years were included as cases ($n=45$). Age- and gender-matched healthy adults with no family history of diabetes were recruited as controls ($n=45$). Participants with chronic illnesses, pregnancy, or regular physical activity were excluded.

Results: Heart rate ($p<0.001$), systolic blood pressure ($p<0.001$), diastolic blood pressure ($p<0.001$), mean arterial pressure (MAP; $p<0.001$), and rate pressure product (RPP; $p<0.001$) all showed statistically significant differences between groups; pulse pressure (PP) did not ($p=0.106$). Body fat percentage ($p<0.001$), visceral fat ($p<0.001$), Cooper 12-minute run test distance ($p<0.001$), estimated VO_2max ($p<0.001$), and fasting blood glucose (FBS; $p<0.001$) were all significantly different. Significant differences in oxidative stress markers were observed: total antioxidant status (TAOS; $p<0.001$) and malondialdehyde (MDA; $p<0.001$).

Discussion: Cases demonstrated significantly higher weight, body mass index (BMI), waist-hip ratio (WHR), body fat percentage, and visceral fat compared to controls. Cardiovascular parameters and fasting blood glucose were significantly elevated in individuals with a family history of T2DM. Cardiorespiratory fitness, assessed by the Cooper 12-minute run test, was significantly lower in cases (estimated VO_2max : 34.29 ± 4.41 mL/kg/min) compared to controls (43.19 ± 1.56 mL/kg/min). TAOS was markedly reduced and MDA was markedly elevated in the case group, indicating heightened oxidative stress in individuals at genetic risk for T2DM.

Conclusion: Apparently healthy adults with a positive family history of T2DM exhibit significantly impaired cardiorespiratory fitness, higher adiposity, and elevated oxidative stress compared to those without such history. Future interventional studies are warranted to determine whether targeted lifestyle modification can attenuate these risk markers in this high-risk population.

Keywords: Obesity, type 2 diabetes mellitus, oxidative stress, cardiorespiratory fitness, family history, cross-sectional study

Introduction

Type 2 Diabetes Mellitus (T2DM) is primarily caused by a combination of defective insulin secretion by pancreatic β -cells and the inability of insulin-sensitive tissues to respond to insulin^[1]. Insulin release and action must precisely meet metabolic demand; hence, the molecular mechanisms involved in the synthesis and release of insulin must be tightly regulated. Defects in any of these mechanisms can lead to pathogenesis of T2DM.

According to the World Health Organization (WHO), diabetes mellitus is a chronic, metabolic disease characterised by elevated levels of blood glucose, leading over time to damage to the heart, vasculature, eyes, kidneys and nerves. Over 90% of diabetes mellitus

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cases are T2DM, marked by deficient insulin secretion by pancreatic islet β -cells, tissue insulin resistance (IR), and an inadequate compensatory insulin secretory response [2]. Patients with T2DM are mostly characterised by obesity or higher body fat percentage, distributed predominantly in the abdominal region. In this condition, adipose tissue promotes IR through various inflammatory mechanisms, including increased free fatty acid (FFA) release and adipokine deregulation. The main drivers of the T2DM epidemic are the global rise in obesity, sedentary lifestyles, high-caloric diets, and population ageing, which have quadrupled the incidence and prevalence of T2DM [3].

The organs involved in T2DM development include the pancreas (α -cells and β -cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue [4]. Evolving data suggest that adipokine dysregulation, inflammation, and abnormalities in gut microbiota and immune function represent important pathophysiological factors [5].

T2DM risk factors include a complex combination of genetic, metabolic, and environmental factors. Although individual predisposition to T2DM due to non-modifiable risk factors (ethnicity and family history/genetic predisposition) has a strong genetic basis, evidence from epidemiological studies suggests that many cases can be prevented by improving modifiable risk factors such as obesity, low physical activity, and an unhealthy diet [6].

Globally, the incidence and prevalence of T2DM vary widely depending on ethnicity and geographical region [7, 8, 9]. Genetic predisposition plays an important part in the risk of developing T2DM. Over the past decade, several genome-wide association studies have demonstrated the complex polygenic nature of T2DM, with most identified loci increasing risk through effects on insulin secretion [10, 11].

Cardiorespiratory fitness, a key physiological marker, is inversely associated with obesity and metabolic disorders. Given the established links between family history of T2DM, obesity, and oxidative stress, the present study aims to evaluate the association of obesity with cardiorespiratory fitness and oxidative stress markers in apparently healthy adults with and without a family history of T2DM.

Materials and Methods

This is a cross-sectional observational study conducted in the Department of Biochemistry, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, from April 2018 to March 2019. The study was approved by the Institutional Ethics Committee of Sree Balaji Medical College and Hospital. All participants provided written informed consent prior to enrolment.

Inclusion Criteria

- Either gender, aged 18 to 60 years.
- First-degree relatives of Type 2 Diabetes Mellitus

patients (case group).

- Age- and gender-matched apparently healthy adults with no family history of diabetes (control group, n = 45).

Exclusion Criteria

Morbid obesity, chronic alcoholism, chronic smoking, pregnancy, lactating women, kyphosis, scoliosis, use of medications preventing sub-maximal exercise, or regular engagement in physical activity, yoga, or biofeedback.

Sample Size

The sample size of N = 90 (45 per group) was calculated based on the expected effect size for group differences in body composition and oxidative stress parameters, with $\alpha = 0.05$ and power = 80%.

Procedure

One day prior to recording, participants were instructed to obtain adequate sleep and abstain from caffeinated beverages, exercise, alcohol, and nicotine for 24 hours. After overnight fasting, participants reported to the Department of Cardiology in the morning. Anthropometric and basal characteristics (height, weight, body mass index [BMI], waist-hip ratio [WHR], body fat percentage, and visceral fat) were recorded after participants had emptied their bladders.

A fasting venous blood sample (5 mL) was collected from the median cubital vein using sodium fluoride tubes for biochemical analysis. Fasting blood glucose (FBS) was measured using a semi-automated analyser. Oxidative stress markers, specifically total antioxidant status (TAOS) and malondialdehyde (MDA), were measured by colorimetric methods. Analytical details including the specific instrument models and assay kit manufacturers are to be confirmed by the corresponding author for reproducibility.

Cardiovascular parameters were recorded at rest: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP = SBP - DBP), mean arterial pressure (MAP = DBP + PP/3), and rate pressure product (RPP = HR $\times$ SBP).

Cardiorespiratory fitness was assessed using the Cooper 12-minute run test. Participants were instructed to cover the maximum distance possible in 12 minutes on a standard running track. Estimated VO_2max (mL/kg/min) was derived using the Cooper formula: $\text{VO}_2\text{max} = (\text{distance in metres} - 504.9) / 44.73$. Observations were analysed using an independent samples t-test with IBM SPSS Statistics, version 25.

Note: Lipid profile data (total cholesterol, LDL, HDL, and triglycerides) were collected in this study and will be reported in a subsequent publication.

Results

Table 1: Baseline and anthropometric parameters of controls and cases

Parameter	Controls (Without FH of T2DM) Mean $\pm$ SD	Cases (With FH of T2DM) Mean $\pm$ SD	p value
Age (years)	37.76 $\pm$ 1.64	37.63 $\pm$ 1.55	0.400
Height (cm)	163.11 $\pm$ 7.19	161.25 $\pm$ 9.26	0.072
Weight (kg)	58.68 $\pm$ 8.19	71.28 $\pm$ 9.69	<0.001*
BMI (kg/m ²)	19.28 $\pm$ 1.95	21.66 $\pm$ 3.06	<0.001*
WHR	0.66 $\pm$ 0.05	0.76 $\pm$ 0.01	0.004*

FH = Family History; T2DM = Type 2 Diabetes Mellitus; BMI = Body Mass Index; WHR = Waist-Hip Ratio. *statistically significant ($p < 0.05$).

Table 1 shows the baseline and anthropometric parameters of controls and cases. There was no significant difference in age ($p=0.400$) or height ($p=0.072$) between groups,

confirming adequate matching. Between controls and cases, significant differences were observed in weight ($p<0.001$), BMI ($p<0.001$), and WHR ($p=0.004$).

Table 2: Cardiovascular parameters of controls and cases

Parameter	Controls (Without FH of T2DM) Mean $\pm$ SD	Cases (With FH of T2DM) Mean $\pm$ SD	p value
HR (bpm)	72.27 $\pm$ 2.84	85.61 $\pm$ 3.05	<0.001*
SBP (mmHg)	122.84 $\pm$ 3.86	134.24 $\pm$ 3.82	<0.001*
DBP (mmHg)	81.24 $\pm$ 3.04	89.54 $\pm$ 2.86	<0.001*
PP (mmHg)	42.68 $\pm$ 3.24	46.54 $\pm$ 5.02	0.106
MAP (mmHg)	74.68 $\pm$ 2.90	80.39 $\pm$ 1.86	<0.001*
RPP	9113.23 $\pm$ 401.64	11955.46 $\pm$ 542.69	<0.001*

HR = Heart Rate; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; PP = Pulse Pressure; MAP = Mean Arterial Pressure; RPP = Rate Pressure Product. *statistically significant ($p<0.05$).

Table 2 presents cardiovascular parameters. Heart rate ($p<0.001$), SBP ($p<0.001$), DBP ($p<0.001$), MAP ($p<0.001$), and RPP ($p<0.001$) were all significantly higher in cases

compared to controls. Pulse pressure did not differ significantly between groups ($p=0.106$).

Table 3: Body fat distribution, cardiorespiratory fitness, and fasting blood glucose

Parameter	Controls (Without FH of T2DM) Mean $\pm$ SD	Cases (With FH of T2DM) Mean $\pm$ SD	p value
FBS (mg/dL)	71.34 $\pm$ 3.79	92.26 $\pm$ 4.02	<0.001*
Visceral Fat (%)	6.44 $\pm$ 0.41	9.25 $\pm$ 2.10	<0.001*
Cooper 12-min run (metres)	2436.89 $\pm$ 69.64	2038.84 $\pm$ 197.12	<0.001*
Estimated VO ₂ max (mL/kg/min)	43.19 $\pm$ 1.56	34.29 $\pm$ 4.41	<0.001*
Body Fat (%)	21.51 $\pm$ 1.32	28.98 $\pm$ 2.38	<0.001*

FBS = Fasting Blood Glucose. Estimated VO₂max derived using Cooper formula: VO₂max = (distance in metres – 504.9) / 44.73. *statistically significant ($p<0.05$).

Table 3 presents body fat distribution and cardiorespiratory fitness data. All parameters differed significantly between groups: body fat percentage ($p<0.001$), visceral fat ($p<0.001$), Cooper 12-minute run test distance ($p<0.001$), estimated VO₂max ($p<0.001$), and FBS ($p<0.001$). Cases

had considerably lower cardiorespiratory fitness (mean estimated VO₂max 34.29 mL/kg/min, classified as 'below average') compared to controls (43.19 mL/kg/min, classified as 'average' for age).

Table 4: Oxidative stress parameters of controls and cases

Parameter	Controls (Without FH of T2DM) Mean $\pm$ SD	Cases (With FH of T2DM) Mean $\pm$ SD	p value
TAOS (mM)	1.06 $\pm$ 0.16	0.42 $\pm$ 0.25	<0.001*
MDA (mM)	7.62 $\pm$ 0.81	12.87 $\pm$ 8.16	<0.001*

TAOS = Total Antioxidant Status; MDA = Malondialdehyde. *statistically significant ($p<0.05$).

Table 4 shows oxidative stress parameters. Between controls and cases, there was a significant difference in TAOS ($p<0.001$) and MDA ($p<0.001$), with cases exhibiting markedly lower antioxidant capacity and higher lipid peroxidation.

Discussion

The present study compared cardiovascular parameters, body composition, cardiorespiratory fitness, and oxidative stress between apparently healthy adults with and without a family history of T2DM. Key findings were that cases had significantly higher weight, BMI, WHR, body fat percentage, and visceral fat; elevated HR, SBP, DBP, MAP, and RPP; lower cardiorespiratory fitness (Cooper test distance and estimated VO₂max); higher FBS; lower TAOS; and higher MDA compared to controls. Pulse pressure did not differ significantly ($p=0.106$). These findings suggest early physiological and metabolic derangements in individuals genetically predisposed to T2DM, even before clinical disease onset.

It is well established that cardiorespiratory fitness is inversely associated with impaired glucose tolerance and diabetes; however, fewer investigations have examined

demographic and behavioural factors associated with cardiorespiratory fitness among adults at high genetic risk. This study demonstrated that, similar to findings in individuals with overt diabetes, individuals with a family history of T2DM and lower physical activity and higher BMI generally exhibited lower cardiorespiratory fitness. This is concerning in that not only may genetic predisposition increase risk for premature cardiovascular morbidity,^[12] but low cardiorespiratory fitness is itself an independent predictor of mortality even after adjusting for comorbidities^[13].

The findings showed that estimates of cardiorespiratory fitness were lower in those with positive family history, consistent with other studies examining diabetes-associated fitness decline^[14]. Both measurement methods have inherent error; the heart rate extrapolation method carries error from the estimate of maximal heart rate (220–age). Jackson *et al.*^[15] showed this formula can overestimate maximal heart rate by up to 22 beats per minute, particularly among hypertensive individuals. The non-exercise prediction used in the present study has been cross-validated in independent samples^[16, 17]. Regular physical activity participation is associated with higher cardiorespiratory fitness, though our

findings did not demonstrate a link between self-reported exercise frequency and fitness, likely reflecting limitations of self-reported physical activity data. Future studies should use objective measures (e.g., accelerometry).

Similar to findings in the general population, weight status was associated with cardiorespiratory fitness among adults at risk for T2DM. Overweight and obese individuals were estimated to have lower cardiorespiratory fitness than normal-weight adults, consistent with the established link between obesity and metabolic disease^[18]. The mean estimated VO₂max for cases in the present study (34.29 mL/kg/min) falls in the 'below average' fitness category, indicating not only genetic risk from family history but also fitness-related risk for adverse health outcomes.

Overall, findings suggest that apparently healthy adults with a family history of T2DM, particularly those who are overweight or obese, may be at increased risk for morbidity and mortality associated with low cardiorespiratory fitness and elevated oxidative stress. Lifestyle modification including regular physical activity is likely to be beneficial in this population^[19, 20, 21]. When promoting physical activity, clinicians may consider tailored counselling approaches such as motivational interviewing and cognitive behavioural therapy, which have shown efficacy in at-risk populations^[22]. Addressing physical activity barriers such as depression, weakness, and low outcome expectations may further improve adherence^[23].

Conclusion

This cross-sectional observational study demonstrates that apparently healthy adults with a positive family history of T2DM exhibit significantly higher adiposity, impaired cardiorespiratory fitness, elevated fasting blood glucose, and greater oxidative stress compared to individuals without such family history. These findings indicate that familial genetic predisposition to T2DM may manifest as early physiological and metabolic alterations, including reduced TAOS and elevated MDA, even in the absence of clinical disease. Future longitudinal and interventional studies are warranted to evaluate whether targeted physical activity and lifestyle modification programmes can attenuate these risk markers in this high-risk population.

Declarations

Ethics Approval: The study was approved by the Institutional Ethics Committee of Sree Balaji Medical College and Hospital, Chennai. All participants provided written informed consent.

Conflict of Interest: The author declares no conflict of interest.

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Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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