Original Article

Pulse wave analyzed cardiovascular parameters in young first degree relatives of type 2 diabetics- a cross-sectional study

Jayesh D. Solanki*1, Hemant B. Mehta, Chinmay J. Shah

Department of Physiology, Govt Medical College, Bhavnagar, Gujarat, India

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A B S T R A C T

Background: First degree relatives (FDR) of type 2 diabetic (T2D) are predisposed for type 2 diabetes mellitus (T2DM) which accelerates cardiovascular aging. Pulse wave analysis (PWA) gives non-invasive measurement of central hemodynamics like central blood pressure (cBP), cardiac output (CO), stroke work (SW) and vascular stiffness like pulse wave velocity (PWV) and augmentation index at heart rate 75 (Aix@75).

Objective: To study PWA derived cardiovascular parameters in FDRs of T2D as compared to controls.

Materials and methods: We enrolled 117 FDRs of T2D and 117 matched controls for a cross-sectional study. We performed PWA using Mobil-o-Graph (IEM, Germany) by oscillometric method to derive cardiovascular parameters which were compared and correlated for significance. P value less than 0.05 was considered statistically significant.

Results: Gender, age, height, weight, body mass index (BMI), physical activity were comparable between groups. FDRs of T2D had significantly higher blood pressure (brachial-systolic 125 vs 118, diastolic 80 vs 77, mean 100 vs 96 mmHg and central- systolic 113 vs 105, diastolic 82 vs 79, pulse pressure 31 vs 28 mmHg), SW (98 vs 90 g/m2), rate pressure product (RPP -113 vs 107), PWV (5.14 ± 4.89 m/s), Aix@75 (30 vs 27) than control. Dependant variables correlated with brachial BP more than age or anthropometric variables. Result did not differ by maternal or paternal inheritance in case group.

Conclusions: Young, sedentary, non-obese FDRs of T2D have adverse cardiovascular profile which is suggested to worsen before or with onset of T2DM and definitely need attention for life style modification as primary prevention.

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1. Introduction

Rise of type 2 diabetes mellitus (T2DM) with worrying future trend for world and India1 is known so as the concept of early onset of diabetes.2 Positive family history is most significant and independent predisposing factor for T2DM.3 It is thought to be, sometimes, a disease of vascular aging with hyperglycemia as late manifestation.4 Cardiovascular aging is early and accelerated once T2DM ensues,5 but whether is it a risk for the same in young first degree relatives (FDRs) of type 2 diabetics (T2D), remains a question. It more so probable if FDR of T2D is sedentary,6 living stressful life. It can be measured non-invasively by pulse wave analysis7 under headings of hemodynamic parameters like central blood pressure (cBP), cardiac output (CO), stroke work (SW), rate pressure product (RPP) and vascular stiffness parameters like augmentation pressure (AP), pulse wave velocity (PWV) and augmentation index (Aix). We tested the hypothesis of early cardiovascular ageing in young FDRs of T2D as compared to matched controls.

2. Materials and methods

2.1. Study design and subjects

We conducted a community based observational study at clinical research laboratory of Physiology department of a government medical college attached to tertiary care teaching government hospital from 18th June 2015 to 25rd April 2016. Prior approval for the study was taken from institutional review board and each participant gave written informed consent. We enrolled, using convenience sampling method, from our institute total 482 apparently healthy subjects with known parental history of T2DM.
and hypertension. After scrutiny we finally had 117 subjects as first degree relatives (FDR) of type 2 diabetic taken as case group. We excluded subjects with family history of hypertension from current study. Of remaining participants, we set to make a control group of 117 subjects matched to case group by age, gender, BMI and physical activity, but with negative family history of T2DM [Fig. 1].

2.2. Inclusion and exclusion criteria

We included FDRs T2D, aged 15 to 35 years, of either sex, not known for any disease, not taking any medical treatment (including anti-diabetic medication), living sedentary life style, ready for written consent. We excluded subjects known to have T2DM, aged more than 35 years or less than 15 years, having hypertension, any acute or chronic cardiovascular diseases, denying written consent, having any disease or drug history, current or ex-smokers or tobacco chewers, trained athletes, subjects using of any alternative system of medicines/life style managements like yoga and mediation. We excluded one subject from analysis after pulse wave recording due to irregular pulse wave rhythm. Criteria for control group were similar as above except absence family history of T2DM.

2.3. Initial assessment and definitions

We personally interviewed all subjects before enrolment. It was in the form of questionnaires including general features, demographic characteristics, height, weight, disease history, drug history, life style intervention used, intake of tea, coffee, alcohol or meal, sleep history and family history of T2DM and hypertension.

Diabetes mellitus was defined as per the American Diabetes Association criteria 2014.7

First degree relative of T2D was defined as subject having either a parent or a grandparent having known T2DM.

Systolic blood pressure less than 140 mmHg and diastolic blood pressure less than 90 mmHg were defined as controlled blood pressure.

2.4. Instrument used

We used portable, PC attached, calibrated and validated instrument Mobil-o-Graph (IEM Gmbh, Stolberg, Germany) owned by Physiology department to record brachial pulse wave. It performs pulse wave analysis based on Oscillometric method. Arterial pulsation generates the pressure oscillations, which are transmitted to blood pressure cuff and measured by transducer to be fed into microprocessor. Computerized software records pulse wave from brachial artery and by a transfer factor derives central aortic pulse wave. It further undergoes point based and area based analysis by computer to derive various cardiovascular parameters.

2.5. Measurement protocol

A blood pressure cuff of appropriate size was chosen based on mid arm circumference (small, medium or large) and applied to left arm using standard protocol. All readings were taken after 10 min of rest, in post absorptive phase with subjects avoiding smoking or alcohol for 12 h before the test, in a calm room avoiding external influences or arm movement.

2.6. Parameters measured

1) Heart rate (HR), body mass index (BMI), body surface area (BSA)
2) Brachial blood pressure (bBP) – systolic (bSBP), diastolic (bDBP), pulse (bPP) and mean (bMBP)
3) Central blood pressure (cBP) – systolic (cSBP), diastolic (cDBP), pulse (cPP)
4) Central hemodynamics– cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVR)
5) Arterial stiffness- augmentation pressure (AP), augmentation index at heart rate 75 per minute (Ali75), reflection magnitude percentage (Rf%), pulse wave velocity (PWV)

2.7 Parameters derived

1) Rate pressure product (RPP) = (heart rate per minute) × (systolic blood pressure) × 10^-2
2) Stroke volume (SV) – cardiac output/heart rate
3) Stroke volume index (SVI) – stroke volume/body surface area
4) Stroke work (SW) = (pulse pressure) × (stroke volume) × 0.0144
5) Total arterial stiffness (TAS) = pulse pressure/stroke volume

2.8. Statistical analysis

Sample size was calculated by Raosoft software (Raosoft, Inc. free online software, Seattle, WA, USA). To have 95% confidence level and 5% precision, a sample size of 138 (Considering either parent diabetic for each subject, size is halved to 62) for population of the city 6 lakhs with 8.7% prevalence of type 2 diabetes mellitus in Asian region was adequate. The data was transferred on Excel spreadsheet and descriptive analysis was expressed as mean ± standard deviation until specifically indicated. All calculations were done by Graph Pad in Stat 3 software (demo version free software of GraphPad Software, Inc, California, USA) and MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). We calculated the statistical significance of differences in mean distribution of various parameters between various groups by Mann-Whitney test or unpaired Student’s t-test for quantitative data and by Normality test for qualitative data. Spearman’s correlation test was used for correlation between parameters — parametric or nonparametric. Statistical significance level was set at \( p < 0.05 \).

3. Results

Case and control group were comparable in age (mean 22 years) and gender (68 males, 49 females in each), with matched height (mean 163 vs 162 cm), weight (mean 58.86 vs 58.38 kg), BMI (Mean 22.13 vs 22.14 kg/m^2), BSA (mean 1.62 vs 1.61 m^2) and physical

![Fig. 1. Study subjects selection-flow chart.](image-url)
activity (5 vs 4 out of 117 in each group) (Table 1). This matching was possible as per selection scheme presented in Fig. 1. Case group had higher values of parameters encompassing brachial blood pressure, vascular stiffness, central blood pressure and central haemodynamics as compared to control group, with all but 5 having statistical significance (Table 1).

The case group of FDR of T2DM, when sub grouped based on maternal versus paternal heritance of disease, showed that most of the parameters had no statistically significant difference between them (Table 2).

In simple and multiple linear regression models we checked correlation between dependant parameters and independent parameters in each group separately.

Correlation of vascular stiffness parameters revealed that height, showed correlation significant only in simple linear regression. PWV showed most consistent positive correlation in either group with age. In case group, PWV correlated positively and significantly with weight, SBP, DBP, MBP, and negatively and significantly with PP. In control group PWV correlation with covariates lacked significance in multiple linear regression model. AP, only in case group correlated negatively with DBP, HR and positively with SBP, having statistical significance. Alx®75 in either group, showed significant positive correlation with HR in either regression model (Table 3).

Correlation of central hemodynamic parameters revealed that height, weight, BMI, MBP and PP correlated with cPP, CO and SW only in simple linear regression model. SBP (positively) and DBP (negatively) correlated significantly, in either model, in majority with cPP, CO and SW, in both groups, more consistently in case than control. Heart rate correlated significantly and negatively with cPP and SW in both group, positively with CO with significance only in case group (Table 4).

4. Discussion

Type 2 diabetes mellitus is modern epidemic with India as one of its epicenters.15 Early onset, rapid progression, delayed detection, poor disease control, poor management, lack of self awareness are the features of our T2D.19 Positive family history is one of the potent but non-modifiable risks to develop T2DM,2 more so with stress, sedentary life style and ignorance of possible primary prevention. Progeria (prenature aging) in young and middle aged individuals is a feature of insulin resistance and increased adipokine production,16 which is possible before onset of type 2 diabetes mellitus. With the trend of early onset T2DM,2 one can predict progeria early in the course in T2DM. FDR of a T2D is at risk for the same. Cardiovascular aging is one of the determinants of lifespan16 and this is early and accelerated in T2D and their siblings. Pulse wave analysis provides a measure to mark this cardiovascular change with sensitivity and specificity. These parameters are affected by age, gender, height, weight, BMI, ethnicity, profession, physical activity.17 Having all these coinfluencers matched, we studied PWA derived cardiovascular parameters in FDRs of T2D as compared to controls.

We found significantly higher peripheral (brachial) and central (aortic) blood pressure in FDRs of T2D as compared to controls. As such similar study from our regions is not noted but FDRs of T2D have abnormal sympathovagal balance and cardiovascular profile even at young age.16 Raised blood pressure indicates vascular
ageing, reduced arterial compliance and increased arterial stiffness\textsuperscript{19} that becomes even more important considering type of matching done and young age of study groups. Cardiac output, peripheral resistance, heart rate was not significantly different between groups. But we used two derived parameters of central hemodynamic, namely rate pressure product\textsuperscript{18} and stroke work\textsuperscript{13} and found that group revealed significantly raised value of these two which indicates extra load on heart and cardiovascular system. Apart from cardiac aging, vascular aging, evident as increased stiffness is also a risk with genetic predisposition to T2DM.\textsuperscript{20} It is even more reliable than blood pressure as it measures the vascular compliance and is more stable variable. FDRs of T2D had raised pulse wave velocity (PWV) which indicates central (aortic) arterial stiffness and raised Aix@75, which indicates peripheral (local) arterial stiffness.\textsuperscript{21} PWV was dependent on and correlated with peripheral blood pressure more than Aix@75 which is contrasting to others but it is in line with the fact that Aix@75 is more useful marker of vascular stiffness in younger subjects, like ours, than PWV.\textsuperscript{22} Most

parameters correlated with brachial blood pressure, which is in line with previous study results\textsuperscript{21} indicating usefulness of brachial blood pressure as a simple gold standard cardiovascular screening test. Age, height, weight and BMI correlated poorly with central hemodynamic and vascular stiffness parameters as opposed to others,\textsuperscript{17,21,23} who found them significant. This may be due to Asian ethnicity,\textsuperscript{24} mean low BMI\textsuperscript{25} and mean low age\textsuperscript{17} as compared to others. We did not find any significant difference of test parameters within case group, based on whether they had paternal or maternal positive family history of T2DM. This is in contrast to few\textsuperscript{26} who found females with maternal history more at risk than the rest. This accelerated ageing of cardiovascular system in FDRs of T2D can be explained by slowed endothelial function, increased stiffness despite normal blood sugar and pressure, reduced arterial compliance and decreased compliance of peripheral arteries.\textsuperscript{27} All these are seen in young adults of T2DM parents\textsuperscript{27} and supports the fact that anatomical change may be late\textsuperscript{27} and screening can detect early changes of subclinical disease.
Being an offspring of a diabetic parent is one of the most significant individual risk factors,\(^2\) which cannot be modified. It is more so due to not only common genetic sharing but also common cultural-environmental factors,\(^2\) whose interaction predispose to T2DM which is showing a trend of ever increasing early onset. Sharing a house with T2DM may offer expected benefits also for improved risk profile for cardiometabolic disorder due to improved health behaviour and closer contact to health care system but this hypothesis fails most of the time.\(^2\) Parameters like RPP, PWV indicate cardiovascular risk which can be used amongst at risk FDRs not only for screening but also for diagnosis and prognosis.\(^3\) Accelerated cardiovascular aging, preceding incident T2DM, may be a link of metabolic syndrome or insulin resistance that progresses to hypertension\(^4\) with its possible aftermaths in years to come. Screening for the same is possible with tool like PWA and parameters like PWV, with life style modifications and other primary prevention being there to be offered to individuals at risk.

### 5. Limitations of study
We had a moderate sample size and cross sectional study which needs further consolidation by large scale vertical study. We intend for follow up of these subjects after five years for next assessment. We did not opt for measurement of biochemical parameters and few untraditional risk factors.

### 6. Conclusion
We found young, non-obese, sedentary FDRs of T2D to have early vascular aging and abnormal hemodynamics as compared to matched controls, dependant on blood pressure with a need of follow up study and implementation of primary prevention by life style modifications to slow, if not to stop, its aftermaths in years to come.

### Conflict of interest
None.

### Contributors
Solanki Jayesh D: Concepts, Design, Definition of intellectual content, Literature search, Clinical studies, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor.
Mehta Hemant B: Concepts, Design, Manuscript editing, Manuscript review.
Shah Chimnay J: Concepts, Design, Manuscript editing, Manuscript review.

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