Sex-Specific, Multi-Modal Assessment of Cardiac Function in Type 2 Diabetes Using the UK Biobank

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Abstract

Type 2 diabetes is a major risk factor for heart failure. Large-scale prospective studies and biobanks are an ideal resource to characterise high-risk populations and identify early markers of disease. Our goal is to quantify cardiac function in men and women with type 2 diabetes and no prior cardiovascular disease. We defined a cohort of type 2 diabetes in the UK Biobank using multiple ascertainment pathways including ICD codes, self-report, and circulating HbA1c. We then extracted ECG and cardiac magnetic resonance image-derived biomarkers related to diastolic function and cardiac autonomic neuropathy, and assessed these relative to reference ranges and current clinical guidelines. We identified 1781 subjects with type 2 diabetes; the cohort was mostly male, overweight, and elderly. We found that males and females with type 2 diabetes exhibit a QTc interval in the upper boundary of normal clinical ranges, with 272 subjects (15%) meeting age- and sex-specific clinical criteria for QTc prolongation, while 668 subjects (38%) had a ventricular rate above 70 bpm. These markers may indicate a higher risk of adverse cardiovascular complications. Left ventricular mass, end-diastolic volume, ejection fraction and wall thickness were found to be within normal ranges, suggesting an absence of perceptible structural remodelling.

1. Introduction

Type 2 diabetes is a complex metabolic disease that is characterised by chronically elevated blood glucose levels. It affects over half a billion adults worldwide, and is responsible for a two- to four-fold increase in cardiovascular disease and a two- to ten-fold increase in sudden cardiac death [1][2][3]. The high prevalence, morbidity, and mortality rates of these tightly interlinked conditions drive the need for effective identification of cardiac deterioration in high-risk populations.

One of the main early-stage hallmarks of type 2 diabetes-induced heart disease is diastolic dysfunction, caused by increased myocardial fibrosis and abnormal active relaxation [4][5][6][7]. An additional complication of diabetes is cardiac autonomic neuropathy (CAN), which causes damage to the nerves in the myocardium and blood vessels [8][9]. Moreover, due to impaired pain reception, CAN often causes cardiac disease to be silent in patients with diabetes, which further motivates the need for clinical vigilance towards early pathophysiological changes in the heart.

ECG and cardiac imaging are common, non-invasive methods that provide valuable insights into subclinical changes in cardiac structure and function. The ECG's cost-effectiveness, widespread availability, and sensitivity to electrophysiological changes make it an ideal candidate for cardiovascular disease screening in the clinic. Indeed, the European Society of Cardiology recommends that clinicians carry out an ECG assessment on patients with diabetes as part of the screening process for heart failure and atrial fibrillation [2]. Cardiac magnetic resonance (CMR) imaging provides a robust assessment of structural and functional abnormalities in the heart. However, its resource-intensive and expensive nature limit its uptake for routine screening, including in patients with diabetes [10]. Large biomedical biobanks represent a valuable resource to conduct population studies at scale. Their aim is to provide researchers with standardised, well-curated biological samples and a wide range of clinical, socio-demographic and lifestyle information on large cohorts of individuals, in an easily accessible and reproducible manner [11]. The UK Biobank contains prospective data of over half a million adults including both ECG and CMR imaging; a rare resource rich both in breadth and depth of data.

In this work, we harness the variety of data available in the UK Biobank to define a cohort of individuals with type 2 diabetes and no prior cardiovascular events, and examine changes in these individuals' cardiac health using ECG and CMR-derived biomarkers. Finally, we discuss these results in the context of reference ranges and current clinical guidelines.

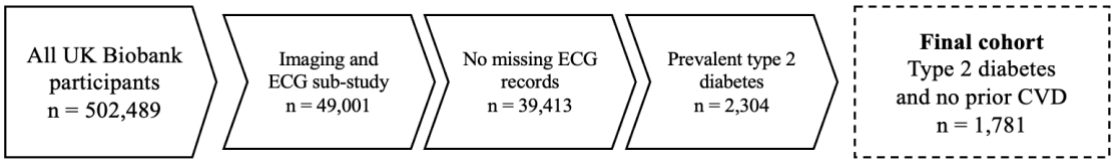

Figure 1: cohort selection flowchart. CVD: cardio-vascular disease.

2. Methods

2.1. Dataset

The UK Biobank study is a multi-centre, prospective study of over 500,000 adults recruited between 40 and 69 years old. We focused on the imaging sub-study, which contains about 10% (~50,000 participants) of the original cohort. These participants underwent a cardiac magnetic resonance (CMR) scan coupled with a 12-lead resting ECG. The UK Biobank is linked to primary care records and hospital episode statistics, where diagnoses are recorded using the International Classification of Diseases (ICD) system along with corresponding dates. General ethical approval was granted for UK Biobank studies by the United Kingdom's National Health Service Research Ethics Service (11/NW/0382). All participants gave written informed consent for their data to be stored and used for research purposes. This study was conducted under UK Biobank Application Number 40161.

2.2. Cohort generation

To ensure comprehensive ascertainment of disease, type 2 diabetes was determined by one or more of the following criteria: ICD-10 codes E11 or E14, ICD-9 codes 250.x0 or 250.x2, positive response to a patient touchscreen questionnaire, or HbA1c $\geq$ 48 mmol/mol (Eastwood et al, 2016). Cardiovascular disease was determined by ICD-9 codes 410-414; 425-428, or ICD-10 codes I20-22; I24-25; I42; I44; I46-50. All participants with prevalent cardiovascular disease at time of imaging, and with incident cardiovascular disease after 21/09/2021, were excluded. Participants with a diagnosis of type 2 diabetes after time of imaging were also excluded. The final cohort consists of eligible participants with prevalent type 2 diabetes and no prevalent or incident cardiovascular disease. Figure 1 summarises the cohort selection process.

2.3. Clinical covariates

We considered the following socio-demographic and clinical variables, recorded on the same date as the imaging assessment: sex, age, height, weight and diastolic blood pressure. We calculated body mass index (BMI) using the ratio of weight in kilograms over squared height in meters, and body surface area (BSA) using Du Bois' formula BSA = 0.007184 x $w^{0.425}$ x $h^{0.725}$ where w is weight in kilograms and h is height in cm. Participants' resting ECGs are stored in individual XML files, which contain the raw signal as well as key automatically computed ECG markers. Here, we extracted ventricular rate and the QTc interval. We also considered the following CMR-derived biomarkers: left ventricular (LV) ejection fraction (EF), LV end-diastolic volume (LVEDV), LV mass, and maximum LV wall thickness across 16 AHA segments. These image-based biomarkers were computed in previous studies and are directly available in the UK Biobank database [12][13]. Indexed LVEDV and LV mass were calculated by dividing each respective marker by BSA.

2.4. Statistical analysis

Continuous variable distributions were assessed for normality using the Shapiro-Wilk test. All variables being non-normal, summary statistics for continuous covariates are reported as distribution median and interquartile range (IQR). Missing data were not imputed. Missing measurements are reported for each variable as counts and percentages of the full sample. Data was processed and analysed using RStudio version 4.1.1 and Python version 3.8.

3. Results and discussion

3.1. Baseline cohort characteristics

Figure 2 reveals the different pathways of ascertainment used to identify prevalent type 2 diabetes at the time of assessment. Cohort size and composition depend on the route(s) of disease ascertainment chosen. This supports the importance of accurately defining cohort exposure factors, such as type 2 diabetes in our case, by using a range of reliable criteria in order to maximise the number of cases identified and to minimise attrition bias, as discussed in [11].

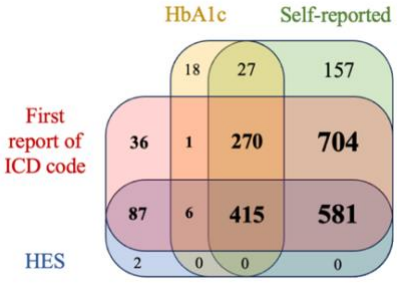

Figure 2: cases of type 2 diabetes at time of imaging assessment (n=2,304). HES: hospital episode statistics, HbA1c: haemoglobin A1C.

After exclusion of prevalent cardiovascular cases, the final cohort consists of 1,781 participants and is mostly male (n=1133, 64%), has a median age of 67 years (IQR: 60-71), a median BMI of 28 kg/m^2 (IQR: 25-32), and a diastolic blood pressure of 79 mmHg (72-85). Old age is likely due to the study design of the UK Biobank; all participants were over 40 years old at recruitment. More than half are clinically classified as overweight, where BMI $\geq$ 25 kg/m^2. Almost half the subjects are above the threshold for normal diastolic blood pressure, suggesting stage 1 hypertension. High diastolic blood pressure has been associated with higher risk of left ventricular diastolic dysfunction in post-menopausal women [14].

3.2. ECG and CMR-derived biomarkers in individuals with type 2 diabetes and clinical implications

Results are summarised in Table 1. Due to inherent baseline differences in male and female hearts, cardiac biomarkers of subjects with type 2 diabetes are reported in sex-specific subgroups. Left ventricular size parameters are lower overall in females compared to males, likely due to expected sex-specific anatomical differences [15]. Ejection fraction and ventricular rate are higher in the female group. Females also have a longer QTc interval compared to males, which again falls within physiological expectations.

	Male median (IQR)	**Female** median (IQR)	**Missing values** N (% of total cohort)
Ventricular rate (bpm)	65 (58-73)	67 (60-74)	0 (0%)
QTc interval (ms)	419 (404-434)	433 (417-447)	0 (0%)
LV mass (g)	103 (90-115)	73 (65-84)	263 (15%)
LVMi (g/m^2)	50 (45-55)	41 (36-45)	263 (15%)
LV maximum regional wall thickness (mm)	8.0 (7.4-8.7)	6.9 (6.3-7.5)	265 (15%)
LVEDV (ml)	142 (122-165)	113 (97-130)	280 (16%)
LVEDVi (ml/m^2)	70 (61-80)	62 (55-70)	280 (16%)
LVEF (%)	54 (50-58)	57 (53-61)	280 (16%)

Table 1: sex-specific median and interquartile ranges of ECG and CMR-derived biomarkers of subjects with type 2 diabetes (full cohort N=1781). LV: left ventricular, M: mass, i: index, EDV: end-diastolic volume, EF: ejection fraction.

Autonomic dysfunction is known to affect heart rate in type 2 diabetic individuals, contribute to left ventricular diastolic dysfunction, and increase overall cardiovascular risk [16][17]. More specifically, CAN increases heart rate in the early stages of disease and later causes it to return to normal, but with reduced variability [8]. This could explain why, despite a large proportion of hypertensive patients, this cohort's ventricular rate lies mostly within normal clinical ranges (60-100 bpm). That being said, 668 (38%) of subjects have a heart rate above 70 bpm, which has been associated with an increase in risk of cardiovascular events in individuals with diabetes [18].

A normal QTc interval ranges between 350 and 440 ms [19]. Clinical thresholds for QTc prolongation, a well-established risk factor for cardiac arrhythmias, are sex- and age-specific: 440 ms for men and 450 ms for women between 40 and 69 years old; 455 ms for men and 460 ms for women of or above 70 years old [20]. In this cohort, male and female QTc intervals lie at the very top end of the normal ranges, with IQRs of 404-434 ms and 417-447 ms, respectively. In adults below 70 years of age, we found that 32 women and 42 men met clinical criteria for QTc prolongation, while 81 women and 117 men above 70 years of age met the criteria, equivalent to 17.4% of females in the cohort and 14.0% of males. A prolonged QTc interval has been showed to be correlated with a higher CAN score in patients with type 2 diabetes [9]. Furthermore, with electrical repolarisation occurring around the same time as mechanical relaxation during diastole, there is a plausible relation between QTc interval and diastolic function. Some studies have suggested links between these two parameters, including in patients with heart failure [21][22]. Therefore, QTc may be indicative of left ventricular diastolic dysfunction in subjects with type 2 diabetes.

In diastolic heart failure, LV mass tends to increase, while LVEDV remains normal [23]. Reference ranges for healthy adults in the UK Biobank, which exclude subjects with diabetes, are reported in [12]. They found that normal LV mass (indexed LV mass) was in range 64-141g (35-70g/m^2) for men and 46-93g (29-55g/m^2) for women, and that normal LVEDV (LVEDVi) was 109-218 ml (60-110 ml/m^2) for men and 88-161 ml (54-94 ml/m^2) for women. In our cohort, measurements of LV mass, LVEDV, and respective indexed values all fell within those normal ranges. The lack of change in LV mass is consistent with a previous study of CMR biomarkers in a cohort of UK Biobank participants with diabetes [24]. Whilst individually, LV mass and LVEDV may not be sufficient to quantify diastolic dysfunction, the ratio of LV mass to LVEDV has been shown to be independently associated with the E/e' ratio, a widely accepted echographic parameter of diastolic function that is commonly used to evaluate HFpEF. Left ventricular hypertrophy (LVH) is another key driver of diastolic dysfunction; it is identified with end-diastolic maximal wall thickness $\geq$ 15.0 mm [25]. Maximum wall thickness measurements in this cohort were well below this threshold.

3.3. Limitations

Currently, only 45% of the UK Biobank has available linked primary care data [11]. Coverage for the entire cohort would increase the number of cases identifiable,

thus increasing statistical power. Comparing the cohort defined in this study to a healthy control cohort within the same setting would also improve clinical relevance and reliability of our results.

4. Conclusion

Using data from the UK Biobank, we have characterised the cardiac health of 1,781 males and females with type 2 diabetes and no prior cardiac events, with a focus on heart rate and biomarkers of repolarisation and left ventricular function. We identified QTc prolongation using sex- and age-specific clinical criteria, and high ventricular rates; these changes may be due to autonomic neuropathy and have been associated previously with a high risk of adverse cardiovascular complications in patients with diabetes. CMR-derived parameters of left ventricular function and structure for males and females were within normal ranges, suggesting the absence of perceptible structural remodelling in this cohort. Our study provides further clinical evidence supporting the need for adequate, sex-specific monitoring of cardiac health in individuals with type 2 diabetes.

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