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Parental brevity linked to cardiometabolic risk in diabetic descendants ☆,☆☆

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ABSTRACT

Background: Non-diabetic offspring from long-lived parents benefit from lowered CV risk. No study investigated the effects of parental lifespan on their progeny when offspring have T2DM. This study assessed CV and metabolic features of T2DM offspring according to parental lifespan.
Patients & Methods: 558 T2DM patients were questioned on parental longevity (paternal and/or maternal lifespan ≥80 years); mean age 66 (11) years; male:female 66:34; divided into 6 groups: long-lived father [LLF] (n = 143); short-lived father [SLF] (n = 262); long-lived mother [LLM] (n = 229); short-lived mother [SLM] (n = 176); long-lived father and long-lived mother [LLF & LLM] (n = 82); and short-lived father and/or short-lived mother [SLF &/or SLM] (n = 323).
Results: Age was similar in [LLF & LLM] and [SLF &/or SLM]. Diabetes duration was longer in [SLF &/or SLM] (p 0.0073). Body composition, hypertension, hepatic steatosis and metabolic syndrome (MetS) were similar in both groups, [SLF &/or SLM] having a higher MetS score: 3.79 (1.12) *vs.* 3.48 (1.12) (p 0.0257). Fasting insulinemia was higher in [SLF &/or SLM] (p 0.0001), who were more insulin resistant (+10%: p 0.0440). HbA_{1c} was higher (+0.36%) in [SLF &/or SLM] (p 0.0138). LDL-C; non-HDL-C; and apoB100 were similar in both groups, whereas HDL-C and apoA-I were higher in [LLF & LLM] (p 0.0233 and p 0.0179). Prevalence and severity of atherogenic dyslipidemia were raised in [SLF &/or SLM], by 53% (prevalence) and 13% (*log*[TG]/HDL-C) (p 0.0172 and p 0.0067).
Conclusion: Bilateral reductions in parental longevity are linked to unfavorable cardiometabolic phenotype in T2DM descendants, with worsened insulin resistance and atherogenic dyslipidemia among 1st-degree offspring.

1. Introduction

Improvement of living standards; spacing of armed conflict; reduced loss of life in battle; food security; advances in medical technology and vaccination; new medications; and better health education in the developed world have significantly improved human longevity over the past decades. Apart from secular improvements in life expectancy related to modifiable external factors, it is now recognized that longevity also runs in families, with offspring from long-lived parents having advantageous cardiovascular (CV) risk profiles in middle age (Jaunin et al., 2009; Meigs, Caldwell, & Albrink, 1965; Terry et al., 2007; Yarnell et al., 2003).

Type 2 diabetes mellitus (T2DM) is an acquired condition of increasing prevalence worldwide, mainly as a result of the obesity/sedentarity pandemics, and is comorbid with the metabolic syndrome (MetS) and insulin resistance (IR). T2DM considerably reduces quality of life, primarily as a result of microvascular complications, and shortens life-expectancy, primarily as a result of macrovascular diseases. T2DM is compounded by the frequent presence of comorbidities which accelerate the occurrence of atherosclerotic CVD, such as hypertension, atherogenic dyslipidemia (AD), chronic subclinical inflammation, chronic kidney disease, and sleep apnea syndrome (Hermans & Fruchart, 2010, 2011; Hermans, Ahn, & Rousseau, 2011, 2012a; Hermans, Ahn, Mahadeb, & Rousseau, 2013).

In the general population, offspring of very long-lived siblings show a lower prevalence in major cardiometabolic conditions, such as hypertension; T2DM; stroke and coronary heart disease (CHD), partially related to a delay in age of onset for cardiovascular disease (CVD), which is not due solely to lesser exposure to conventional CV risk factors (Jaunin et al., 2009; Meigs et al., 1965; Terry et al., 2007; Yarnell et al., 2003). No study to date has investigated the effects of

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parental lifespan on their progeny when the offspring suffer from T2DM. It is not known in particular whether having one (father or mother) or both parent(s) reaching or not an advanced age alters the cardiometabolic risk (CMR) of diabetic descendants. The aim of this study was to define the cardiovascular and metabolic features of T2DM offspring according to parental longevity or brevity.

1.1. Patients and methods

The study design was cross-sectional and included 558 consecutive adult (>18 years) patients with T2DM, who were questioned on parental longevity, defined as paternal and/or maternal lifespan ≥80 years, based on age(s) at the time of parental death(s), or age at the time of the study for alive parent(s). Mean age was 66 (11) years; with 84% North-Caucasians; 6% North-Africans; and 6% sub-Saharan Africans. Age at diabetes diagnosis was 52 (12) years. The male:female ratio was 66:34. A family history for DM was present in 49%, and of parental early-onset CHD (EOCHD) in 12%.

One-hundred and fifty-three patients were excluded based on the following: (*i*) patients had one or two alive parent(s) aged <80 years; (*ii*) patients had one or two parent(s) whose age at death was unknown; (*iii*) unidentified biological parent(s); (*iv*) one or two parent(s) died prematurely (i.e. deceased <50 years; from any causes) and/or suffered from familial (i.e. hereditary) hypercholesterolemia (FH); (*v*) parent(s) died before the age of 80 years as a result of human or natural accident or disaster; homicide; suicide; direct or collateral war-related fatality; or other fatal trauma.

The remaining 405 patients were divided in six groups:

1. *long-lived father* [**LLF**] ($n = 143$), regardless maternal longevity;
2. *short-lived father* [**SLF**] ($n = 262$), regardless maternal longevity;
3. *long-lived mother* [**LLM**] ($n = 229$), regardless paternal longevity;
4. *short-lived mother* [**SLM**] ($n = 176$), regardless paternal longevity;
5. *long-lived father* and *long-lived mother* [**LLF & LLM**] ($n = 82$);
6. *short-lived father* and/or *short-lived mother* [**SLF &/or SLM**] group ($n = 323$), composed of:
   - patients with *biparental brevity* ($n = 115$);
   - patients with *paternal longevity but maternal brevity* ($n = 61$);
   - patients with *maternal longevity but paternal brevity* ($n = 147$).

In all T2DM offspring, the following socio-demographic indices; lifestyle indicators; anthropometric measures and clinical characteristics were evaluated: age; gender; education (dichotomized as below high-school *vs.* otherwise); diabetes duration; presence of 1st-degree familial history (mother and/or father and/or siblings) for diabetes mellitus (DM), and/or for a 1st-degree familial history of EOCHD, defined as occurrence of an inaugural CVD event <55 years (men) and <65 years (women), with exclusion of FH. Abnormal glucose homeostasis or diabetes diagnosed in the course of terminal parental illness and/or DM diagnosed in elderly parents was not considered as sufficient evidence for familial history of the common form of DM, neither were parental histories for type 1 DM or monogenic diabetes.

In the T2DM offspring, smoking history; ethanol intake were determined, as well as current medications: (*i*) oral "antidiabetic" (i.e. glucose-lowering) drugs (OAD); incretin-based therapies (IBT; *dipeptidyl peptidase* type 4 (DDP-4) inhibitors or glucagon-like peptide (GLP-1) receptor agonists); (*ii*) insulin; (*iii*) CV drugs [blood-pressure (BP)-lowering; aspirin; and lipid-lowering drugs (LLD: statins; fibrates and/or ezetimibe).

Weight; height; waist circumference; and body mass index (BMI) were measured, together with total body fat; visceral fat; and skeletal muscle mass [BodyFat Analyzer, Omron BF 500; Omron Healthcare Europe B.V., Hoofddorp, The Netherlands). Non-alcoholic fatty liver was considered in the presence of ultrasonic hyper-reflectivity, in the absence of etiological factors associated with hepatic steatosis, including excess ethanol intake. Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg and/or current treatment with BP-lowering drug(s).

The presence of diabetic retinopathy (DRP) was diagnosed following retinal examination by an experienced ophthalmologist and/or fluorescein angiography. The presence of diabetic neuropathy (DNP) was diagnosed by clinical examination (knee and ankle reflexes; Semmes–Weinstein monofilament test) and confirmed by lower-limbs electromyography. Glomerular filtration rate was estimated (eGFR) using the *Modified Diet in Renal Disease equation* (Levey et al., 1999). A diabetic nephropathy (DN) was considered in the presence of microalbuminuria and macroalbuminuria (urinary albumin excretion 30–299 (micro-) and ≥300 μg.mg creatinine^{-1}.1.73 m^2 (macro-), from first-morning urine sample, after exclusion of non-diabetic causes of albuminuria or proteinuria). Regardless of (micro) albuminuria, DN was also considered in the presence of reduced kidney function, i.e. eGFR <60 mL/min/1.73 m^2. As the latter may not *de facto* be attributable to DM, any eGFR-identified overt nephropathy was considered to represent DN, unless a confirmed diagnosis of non-specific, non-diabetic nephropathy was made.

Coronary artery disease (CAD) was defined from medical history (myocardial infarction, angioplasty, stenting, revascularization surgery and/or significant coronary stenosis confirmed by angiography); systematic review of procedures; and/or following screening with exercise testing, echocardiography, magnetic resonance imaging, or other subclinical disease imaging techniques. Stroke was defined according to *UK Prospective Diabetes Study* (UKPDS) criteria: any neurological deficit ≥1 month, without distinction between ischemic, embolic and haemorrhagic events (Stevens et al., 2004). Peripheral artery disease (PAD) was diagnosed from medical history of lower-limb(s) claudication; clinical or imaging evidence for ischemic diabetic foot; history of angioplasty, stenting, revascularization surgery; and/or lower-limb artery stenosis at Doppler ultrasonography or angiography.

The following laboratory variables were measured: HbA_{1c}; fasting glucose and insulinemia (after 48 h of glucose-lowering drug(s) discontinuation); fasting lipids (total cholesterol (C), high-density lipoprotein (HDL)-C, triglycerides (TG); low-density lipoprotein cholesterol (LDL-C), computed using Friedewald's formula, and non-HDL-C (by subtracting HDL-C from total C)); apolipoproteins A-I (apoA-I) and B_{100} (apoB); $_{hs}$CRP; uric acid; fibrinogen; *sex hormone-binding globulin* (SHBG); serum iron; and ferritin.

Atherogenic dyslipidemia (AD) was defined as the combination of low HDL-C (<40 mg.dL^{-1} (males); <50 mg.dL^{-1} (females)) and high fasting TG (≥150 mg.dL^{-1} for both genders), based on metabolic syndrome (MetS) cutoffs for non-LDL lipids (*see below*) (Hermans & Fruchart, 2010; Hermans et al., 2011). AD prevalence, as *dichotomous state*, was established as the combined occurrence of low HDL-C plus high TG, from last available fasting TG and HDL-C measurements prior to LLD implementation [LLD(s)-treated patients], or from current fasting TG and HDL-C [LLD-naïve patients], respectively. AD severity was quantified as *continuous variable* using the *log*[TG]/HDL-C ratio, from *current* fasting lipids, without gender dichotomy. Normal values and range for *log*[TG]/HDL-C are provided in (Hermans, Ahn, & Rousseau, 2010, 2012b).

The presence of a MetS was defined as a score ≥3/5 for the five following items: (*i*) impaired fasting glucose or diabetes; (*ii*) hypertension; (*iii*) enlarged waist; (*iv*) elevated fasting TG; and (*v*) decreased HDL-C, according to the *IDF-NHLBI-AHA-WHF-IAS-IASO* definition (Alberti et al., 2009). Homeostasis Model Assessment (HOMA) of insulin sensitivity and β-cell function was previously detailed (http://www.dtu.ox.ac.uk). Values of insulin secretion (HOMA B; normal value 100%) were plotted as a function of insulin sensitivity (HOMA S; normal value 100%), defining a *hyperbolic product* area [B × S] (unit: %^{2}; normal value 100%, corresponding to 10^4 %^{2}), which represents the true, underlying β-cell function. [B × S]