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Effect of fitness on incident diabetes from statin use in primary prevention

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ABSTRACT

Objective: To assess the effect of cardiorespiratory fitness on the association between the initiation of statin therapy and incident diabetes.
Patients and methods: In a prospective observational study, we studied 6519 generally healthy men and 2334 women with two preventive health examinations from December 15, 1998 through December 18, 2013 which included measurement of fitness levels, statin therapy, risk factors for diabetes, and incident diabetes.
Results: 93 cases of incident diabetes occurred during an average follow-up of 3.0 years. After multivariable adjustment, an increased odds of incident diabetes with statin use was observed in those patients with impaired fasting glucose at baseline (odds ratio [OR]: 2.15, [95% CI:1.26 to 3.67]), but not among individuals with normal glucose levels (OR:1.85, [95% CI: 0.76 to 4.52]). Cardiorespiratory fitness attenuated but did not eliminate the increased risk of incident diabetes with statin use.
Conclusion: In a population of relatively healthy patients, statin use was not associated with incident diabetes in patients with normal fasting glucose at baseline. However, it was associated with incident diabetes in those patients with impaired fasting glucose at baseline, though this risk was substantially reduced by increasing fitness. In addition, increasing cardiorespiratory fitness was inversely associated with incident diabetes whether or not a patient was treated with a statin.

1. Introduction

Based on data from one large randomized clinical trial (RCT) and several meta-analyses, the use of statin medications has been associated with a modest increase in the risk of incident diabetes [1–5]. Consequently, in 2012, the FDA announced that statin medication labeling would be required to include the warning that incident diabetes and increased blood glucose were possible with statin use.

The absolute benefits of statin use in secondary prevention of cardiovascular events have been robustly demonstrated and persist even in those patients who develop diabetes on statin medication [2,3]. However, new concern exists when using statin medications in the setting of primary prevention in which the balance of incident diabetes versus cardiovascular disease prevention may be less favorable. Results from the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study [6], a primary prevention trial using statins in patients with an elevated marker of inflammation, demonstrated two important findings. First, among those individuals randomized to statin treatment, there was an increased risk of incident diabetes (HR 1.25, 95% CI 1.09–1.49) [4]. Second, this increased risk was limited to those with one of four baseline risk factors (metabolic syndrome, impaired fasting glucose, body mass index (BMI) $\geq$30 kg/m^2, or HbA1C >6%) [4].

Cardiorespiratory fitness (CRF) is inversely associated with the development of diabetes and its risk factors such as metabolic syndrome, obesity and increased waist girth [7–10]. The impact of

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fitness on incident diabetes with statin use is not known. The goal of this study was to evaluate the impact of measured cardiorespiratory fitness on incident diabetes associated with statin use in a preventive care population without known cardiovascular disease.

2. Methods

2.1. Study population

The Cooper Center Longitudinal Study (CCLS) is a large, prospective cohort followed for over 40 years. The CCLS data come from the Cooper Clinic, a preventive medicine practice initiated in 1970. Patients are either self-referred or are referred by their employers for preventive health examinations that include a standardized medical examination by a physician, anthropometric measurements, fasting laboratory studies, a maximal treadmill exercise test for objectively measured CRF and additional studies as clinically indicated. The participants are generally non-Hispanic whites with a high education level and of middle to upper socioeconomic strata. The CCLS database and privacy precautions are maintained by The Cooper Institute. Participants provided written informed consent for the use of their data for research, and data collection protocols and informed consent are reviewed and approved annually by Institutional Review Board at The Cooper Institute.

The present study examined the association between statin use and the incidence of diabetes in men and women who were examined at the Cooper Clinic (Dallas, Texas) from December 1998 to December 2013 for two preventive health visits. A sample of 10121 CCLS participants were identified who had at least two complete examinations with treadmill testing and completed medication data entry (referred to as the index visit and visit two). Participants were excluded if they 1) were receiving statin therapy at the index visit, 2) had known history of diabetes, 3) had a fasting blood glucose ≥126 mg/dL, 4) use of diabetes medication, or 5) known cardiovascular disease (CVD). As a result, a total of 6519 men and 2334 women aged 20–90 years were included in the analytic sample.

2.2. Clinical evaluation

Information about prescription and over-the-counter medications as well as supplements (medication name, dose and dosing interval) was recorded for each participant from the physician's medical report for each clinic visit. Medication history and the remainder of the medical history were reviewed and confirmed by the clinic physician. Patients were divided into two groups: those patients who were not on a statin medication at the index visit or at visit two ("Never Statin" group) and those patients who were not on a statin medication at the index visit but were on a statin medication at visit two ("Started Statin" group).

Height and weight were measured using a standard clinical scale and stadiometer. BMI was calculated as weight/height^2 (kg/m^2). Waist circumference (cm) was measured at the umbilicus level following a normal exhalation. Seated resting blood pressure was obtained with a mercury sphygmomanometer using the American Heart Association protocol. Venous blood samples are collected following a 12-hour fast. Cooper Clinic laboratory technicians analyzed blood chemistry using standard procedures. Key laboratories for this study included glucose, total cholesterol, LDL-cholesterol, and HDL-cholesterol. Metabolic syndrome was defined according to American Heart Association and National Heart Lung and Blood Institute 2005 consensus criteria [11]. Endpoints of self-reported diabetes, use of diabetes medications, and/or blood glucose level ≥126 mg/dl were combined to define the categorical diabetes outcome variable. The follow-up period was defined as the time between the index visit and visit two.

2.3. Cardiorespiratory fitness measurement

CRF was objectively measured according to maximal time on a treadmill test using the modified Balke protocol as previously described [12]. Time on the treadmill with this protocol is highly correlated with measured maximal oxygen uptake in both men (r = 0.92) [13] and women (r = 0.94) [14]. Maximal MET levels (1 MET = 3.5 mL O_2 kg^{-1} min^{-1}) were estimated using the American College of Sports Medicine equation (3.5 + (0.1*speed) + (1.8*speed*grade)) from the final treadmill speed and grade [15]. CRF was also categorized into age- and gender-specific quintiles based on the CRF distribution of the sample. These quintiles were then combined into three, mutually exclusive fitness groupings: "low fit": quintile 1; "moderate fit": quintiles 2–3; "high fit": quintiles 4–5 as has been the standard in this cohort.

Table 1
Characteristics of participants at index visit and visit 2 stratified by statin use at visit 2.

	Index visit			Visit 2		
	Never Statin group	Started Statin group	p-value	Never Statin group	Started Statin group	p-value
Participants	7591	1262		7591	1262	
Men	5448 (72)	1071 (85)	<0.001			
Age (y)	47.6 (8.8)	51.7 (8.4)	<0.001	50.6 (9)	55.5 (8)	<0.001
Current smoker	751 (11.9)	141 (12.8)	0.423	597 (9.5)	99 (9.1)	0.695
Body mass index (kg/m^2)	25.9 (3.9)	27.0 (3.7)	<0.001	26.0 (3.8)	27.2 (3.9)	<0.001
Body mass index ≥30	1042 (13.7)	222 (17.6)	<0.001	1018 (13.4)	259 (20.3)	<0.001
Waist girth (cm)	87.9 (13.0)	92.2 (11.3)	<0.001	87.4 (13.0)	92.6 (11.5)	<0.001
Hypertension	827 (10.9)	259 (20.5)	<0.001	974 (12.8)	340 (26.9)	<0.001
Systolic blood pressure (mm Hg)	119.1 (13.5)	124.9 (14.6)	<0.001	119.0 (13.5)	122.7 (13.2)	<0.001
Diastolic blood pressure (mm Hg)	80.4 (9.4)	83.7 (10.1)	<0.001	79.9 (9.1)	81.0 (9.0)	<0.001
Total cholesterol (mg/dL)	195.7 (33.1)	224.2 (36.2)	<0.001	197.4 (33.8)	165.2 (30.9)	<0.001
HDL cholesterol (mg/dL)	54.7 (16.0)	52.2 (15.3)	<0.001	56.3 (17.0)	53.7 (14.6)	<0.001
LDL cholesterol (mg/dL)	119.2 (30.0)	144.2 (31.4)	<0.001	119.3 (30.0)	89.5 (24.5)	<0.001
Triglycerides (mg/dL)	111.0 (77.4)	142.6 (100.4)	<0.001	110.4 (80.9)	112.2 (107.0)	0.573
Glucose (mg/dL)	94.8 (8.6)	97.5 (8.5)	<0.001	94.4 (10.4)	97.3 (9.8)	<0.001
Cardiorespiratory fitness (MET)	11.5 (2.3)	11.1 (2.1)	<0.001	11.5 (2.3)	10.9 (2.2)	<0.001
FRS 10-yr risk (%)	5.5 (4.3)	9.0 (5.6)	<0.001	6.1 (4.7)	6.0 (4.2)	0.406
Metabolic Syndrome	1078 (14.2)	38 (25.2)	<0.001	986 (13.0)	238 (18.9)	<0.001

Data are presented as numbers (percentage) of patients or mean (SD).
HDL = high density lipoprotein; LDL = low density lipoprotein; MET = Metabolic equivalent; FRS= Framingham risk score.