Journal of Diabetes and Its Complications 28 (2014) 559–564

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Effects of lipids and lipoproteins on diabetic foot in people with type 2 diabetes mellitus: A meta-analysis

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ARTICLE INFO

Article history:
Received 1 March 2014
Received in revised form 29 March 2014
Accepted 1 April 2014
Available online 13 April 2014

Keywords:
Diabetic foot
Lipids
Lipoproteins
Meta-analysis
Risk factors

ABSTRACT

Background: To conduct a meta-analysis of case–control studies to determine the effects of lipids and lipoproteins on morbidity of diabetic foot in adults with type 2 diabetes.
Methods: We searched the PubMed and EMBASE to identify eligible studies. The Newcastle–Ottawa Quality Assessment Scale was used to determine the quality of selected studies. We assessed the strength of associations using standardized mean differences with 95% confidence intervals.
Results: A total of 4 articles were found. Decreased HDL-cholesterol had a significant association with diabetic foot susceptibility in fixed-effects model, but no significant associations were found between diabetic foot and LDL-cholesterol, TC or TG levels.
Conclusions: Our results suggested that decreased HDL-cholesterol was associated with diabetic foot, so possible measures to prevent diabetic foot should include targeting increases in HDL-cholesterol.

1. Introduction

The World Health Organization reports that more than 347 million people worldwide have diabetes (Danaei et al., 2011). Patients with diabetes mellitus are at increased risk of foot disease, and lower extremity peripheral arterial disease is nearly twice as high in people with diabetes as in people without diabetes (9.5% vs. 5% prevalence) (Gregg et al., 2004). Clinically, diabetic foot is an important, long-standing complication that is associated with increased morbidity and mortality of patients with diabetes mellitus. About 15%–25% of patients with diabetes will experience diabetic foot in their lifetime (Kalish & Hamdan, 2010). Diabetic foot ulcers are the main reason for nontraumatic amputations; about 85% of amputations are preceded by a foot ulcer as the cause of a severe infection or gangrene (Apelqvist, Bakker, van Houtum, Nabuurs-Franssen, & Schaper, 2000).

Diabetes is a disease of impaired glucose metabolism as well as disturbed lipid metabolism (Shafrir & Raz, 2003). It is associated with a twofold to threefold increased risk of accelerated atherosclerosis, partly due to diabetic dyslipidemia, which is characterized by low plasma levels of high-density lipoprotein cholesterol (HDL-cholesterol), elevated triglycerides (TGs), and a predominance of small, dense low-density lipoprotein cholesterol (LDL-cholesterol) particles (Lamarche et al., 1997). Diabetes affects almost all lipids and lipoproteins, and chronic dyslipidemia is common in diabetes patients. Lipoproteins are a proven independent discriminating risk factor for coronary artery disease, cerebrovascular disease, and peripheral vascular disease (Unluhizarci, Muhtaroglu, Kabak, Bayram, & Kelestimur, 2006).

To the best of our knowledge, no meta-analysis has focused on the effects of lipids and lipoproteins on the morbidity of diabetic foot. Moreover, studies addressing the correlation between lipoprotein levels and the prevalence of diabetic foot ulcerations are scarce and results on the association are conflicting and inconclusive. Given the important effect of lipids and lipoproteins on the occurrence, progress and prognosis of diabetic foot, we performed a meta-analysis of all published studies to determine the relationship between lipoprotein and the prevalence of diabetic foot ulcerations.

2. Material and methods

2.1. Search strategy and study selection

To conduct this meta-analysis, we performed a search in PubMed and EMBASE for all studies published through September 2013 (inclusive). Keywords used in our computerized literature searches included: diabetes, lipid, lipoprotein, cholesterol, ulcer, foot, humans and diabetic foot. To ensure a high degree of study comparability, only trials with matched clinical and anthropometric parameters were

Conflict of Interest: The authors declare that they have no conflict of interest.

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http://dx.doi.org/10.1016/j.jdiacomp.2014.04.002
1056-8727/

Table 1
Demographic characteristics of patients in the included studies.

Study		Eren et al.	Gazzaruso et al.	Gonzalez et al.	Erdogan et al.
Year		2013	2012	2010	2010
Location		Turkey	Italy	Spain	Turkey
Sample sizes	Cases	$n = 27$	$n = 70$	$n = 89$	$n = 50$
	Controls	$n = 27$	$n = 52$	$n = 109$	$n = 34$
Age (years)	Cases	55.2 ± 8.4	55.3 ± 6.7	66.5 ± 10.7	59.82 ± 10.55
	Controls	56.2 ± 12.9	55.3 ± 6.1	68 ± 10.4	57.41 ± 9.53
Gender (male/female)	Cases	11/16	38/32	35/29	26/24
	Controls	18/9	27/25	59/50	10/24
BMI (kg/m^2)	Cases	27.2 ± 5.3	29.1 ± 4.5	29.9 ± 5.89	28.32 ± 5.81
	Controls	28.0 ± 2.9	29.3 ± 4.5	30.6 ± 5.69	29.82 ± 5.50
Duration of diabetes (years)	Cases	14.5 ± 9.8	11.8 ± 7.7	14.8 ± 10.5	12.92 ± 6.52
	Controls	10.5 ± 8.5	9.0 ± 6.1	11.8 ± 8.6	10.02 ± 5.74
TG (mmol/L)	Cases	1.8 ± 1.1	1.8 ± 0.8	1.85 ± 1.22	1.87 ± 1.05
	Controls	2.3 ± 1.6	1.8 ± 0.9	1.51 ± 1.03	1.93 ± 1.01
TC(mmol/L)	Cases	–	5.2 ± 0.7	5.20 ± 1.56	4.41 ± 1.32
	Controls	–	5.2 ± 0.7	5.12 ± 1.04	4.72 ± 1.02
LDL-cholesterol (mmol/L)	Cases	2.6 ± 0.8	3.2 ± 0.7	3.43 ± 1.02	2.75 ± 1.08
	Controls	3.1 ± 0.9	3.2 ± 0.7	3.37 ± 1.18	3.04 ± 0.90
HDL-cholesterol (mmol/L)	Cases	0.8 ± 0.3	1.2 ± 0.2	1.18 ± 0.32	0.94 ± 0.36
	Controls	1.0 ± 0.2	1.2 ± 0.2	1.22 ± 0.39	1.06 ± 0.31
HbA1c (%)	Cases	10.6 ± 2.7	7.3 ± 1.5	8.13 ± 1.72	9.76 ± 0.31
	Controls	11.1 ± 2.2	7.5 ± 1.5	7.31 ± 1.46	12.1 ± 2.81

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

included. In addition, we manually reviewed the reference lists of eligible trials to ensure that all appropriate studies were included.

The search retrieved 449 articles that were included if they fulfilled the following selection criteria: (1) study aimed to investigate the relationship between lipoprotein (LDL-cholesterol, HDL-cholesterol, total cholesterol or TG) and diabetic foot ulcer (DFU); (2) case–control study design; (3) no interventions (e.g., patient education, drug treatment, nursing care); (4) lipid parameters available; and (5) controls were matched diabetic patients without foot ulcer rather than healthy controls.

2.2. Data extraction

The following data were systematically abstracted from included studies: title, first author name, publication date, design, sources, inclusion and exclusion criteria, sample size, participant characteristics, list and values of variables (LDL-cholesterol, HDL-cholesterol, total cholesterol, TGs) (Table 1). Outcomes were included only for studies in which lipid and lipoprotein data were available.

2.3. Quality appraisal of the included research

Two investigators (Pei and Lu), independently assessed the methodological quality of included studies using the Newcastle–Ottawa quality assessment scale (NOS) for case–control studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), which contains nine items (one point for each, for a total of nine points) categorized into three major categories: (1) selection: adequate definition of cases, representativeness of the cases, definition of controls; (2) comparability: controls matched to cases on age and sex and controls matched by other confounding factors; and (3) exposure: ascertainment of exposures using the same methods to ascertain exposure for cases and controls and the same nonresponse rate in both groups. For each outcome of interest, validity scores were evaluated as follows: ≤5, low quality; 6–7, medium quality; and 8–9, high quality.

2.4. Statistical analysis

Statistical analyses used Stata 10.0 (Stata Corporation, College Station, TX). Pooled standardized mean differences (SMD) with 95% confidence interval (CI) were used to assess association strength between TG, total cholesterol (TC), LDL-cholesterol, HDL-cholesterol and diabetic foot, and calculated by random-effects and fixed-effects models. Statistical significance of pooled SMD was determined with a Z-test, and $P < 0.05$ was considered significant. Statistical heterogeneity among studies was assessed with a Q-test. The I^2 statistic was used to estimate heterogeneity quantitatively (Higgins, Thompson, Deeks, & Altman, 2003) with I^2: <50% = low heterogeneity; 50%–75% = moderate heterogeneity; and >75% = high heterogeneity.

3. Results

3.1. Characteristics of studies

A total of 449 articles were found using the search words. Among these, 4 (Erdogan et al., 2010; Eren et al., 2013; Gazzaruso et al., 2012; Gonzalez et al., 2010) met the preset inclusion criteria, with 236 cases and 222 controls included for pooled analysis (Fig. 1, Table 1). The most common reason for study exclusion was participation in a study intervention (drug treatment, dressing or care). All included studies had a case–control design and were conducted in Europe. We were unable to obtain TC data from the study by Eren et al. The number of patients in each trial ranged from 27 to 89, and most controls were sex, age and geographically matched.

3.2. Quality assessment

The results of quality assessment using the NOS for case–control studies were in Table 2. The mean overall score was 7 of 9 (2.25/4 for selection, 1.75/2 for comparability, 3/3 for exposure). All studies reported that diagnoses of cases and controls were based on criteria and clinical records, and thus all studies were assigned points for “adequate definition of cases” and “definition of controls.” Only a single study reported consecutive participants; an additional point was assigned to this case for representativeness. Lipid index was identified by serological methods, so three additional points were assigned to all studies for “ascertainment of exposure,” “same method to ascertain cases and controls,” and “nonresponse rate.” Overall, scores of included studies ranged from 6 to 8, with only one defined as high quality.