European Journal of Integrative Medicine 8 (2016) 213–218

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/eujim

Research paper

Serum lycopene is inversely associated with long-term all-cause mortality in individuals with rheumatoid arthritis: Result from the NHANES III

Guang-Ming Han[a,b,c,1,*], Xiao-Feng Han[a,1,*]

[a] Wuxi Medical School, Jiangnan University, Wuxi, Jiangsu 214122, PR China
[b] Nebraska Department of Health and Human Services, Lincoln, NE, USA
[c] Department of Epidemiology, University of Nebraska Medical Center, Omaha, NE, USA

ARTICLE INFO

Article history:
Received 13 August 2015
Received in revised form 31 August 2015
Accepted 12 October 2015

Keywords:
Lycopene
mortality
rheumatoid arthritis

ABSTRACT

Introduction: Increased oxidative stress and/or chronic inflammation may play important roles in the high mortality of individuals with rheumatoid arthritis (RA). As a natural antioxidant, lycopene can alleviate oxidative stress and decrease inflammation. Therefore, we hypothesized that lycopene has a potential to reduce the risk of mortality in individuals with RA.

Methods: 694 RA participants aged 20 years and older from the third National Health and Nutrition Examination Survey were divided into three groups by the tertile rank method according to their serum concentration of lycopene. These participants were followed-up from the date of interviews (1988–1994) to December 31, 2011 for mortality. Mortality, survival functions and hazard ratios of mortality were compared between these three tertile groups.

Results: The mortality of participants was significantly lower for the third tertile group (46.4%, 95% CI: 40.1–52.7) compared to the first tertile group (66.5%, 95% CI: 60.4–72.6) and the second tertile group (60.0%, 95% CI: 53.6–66.4%) among participants with RA. There was a significant survival difference between the third tertile group and the first tertile group (Log rank $p < 0.0001$). After adjusting for demographic and other risk factors, RA participants in the third tertile group had a significantly reduced hazard ratio for all-cause mortality (HR = 0.631, 95% CI: 0.433–0.918) compared to RA participants in the first tertile group.

Conclusion: These findings from a nationally representative sample indicate that serum lycopene has a significant association with long-term all-cause mortality in individuals with RA.

Published by Elsevier GmbH.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by excessive productions of oxidative stress and/or chronic inflammation that leads to functional joint impairments and increased mortality [1,2]. The mortality in patient with RA has decreased over past decades due to earlier diagnosis, more aggressive and efficient therapies; however, it still remains higher in patients with RA compared to the general population [3–5]. Although the reasons for the high mortality are not entirely clear, accumulative epidemiologic evidence supports that increased oxidative stress and/or chronic inflammation may play important roles in the high mortality of individuals with RA [6–10].

As a natural antioxidant, lycopene is mainly enriched in tomatoes and other vegetables or fruits, such as red carrots and watermelons. Accumulative evidence shows that alleviating oxidative stress and decreasing inflammation are the main functions of lycopene [11–15]. Furthermore, lycopene has been found to reduce mortality in the general population [16,17], in patients with Alzheimer's disease [18], obstructive lung function [19] and cardiovascular disease [20].

Given the excessive production of oxidative stress and/or chronic inflammation in patients with RA, we hypothesized that lycopene has a potential to reduce the risk of mortality in individuals with RA. To our knowledge, no study has investigated the effect of lycopene on mortality in patients with RA. For this reason, we explored the association between lycopene and mortality in patients with RA from

* Corresponding author.
E-mail addresses: ghan54321@gmail.com, guangming.han@nebraska.gov (G.-M. Han), xfenghan@126.com (X.-F. Han).
[1] These authors equally contributed to this work.

http://dx.doi.org/10.1016/j.eujim.2015.10.003
1876-3820/Published by Elsevier GmbH.

the third National Health and Nutrition Examination Survey (NHANES III).

2. Subjects and methods

2.1. Study population

The data used in this study were obtained from the NHANES III from 1988 to 1994. The survey's design and procedures have been published in the previous work [21]. In brief, the NHANES III are conducted by the National Center for Health Statistics of the Center for Disease Control and Prevention to assess the health and nutrition conditions of adults and children in the US. The study population in this study is a representative sample of civilian, non-institutionalized individuals selected by using a multistage, stratified sampling design. The data collection in NHANES III included a home interview and a followed physical examination. The Center for Disease Control and Prevention institutional review board approved the survey; in addition, before participants took part in the study, they all signed informed written consent forms.

Participants were defined as patients with rheumatoid arthritis (RA) if participants fulfilled at least four criteria of the American College of Rheumatology (ACR, 1987 revised criteria) for diagnosis of RA: morning stiffness (criterion 1), arthritis of 3 or more joint areas (criterion 2), arthritis of hand joints (criterion 3), symmetric arthritis (criterion 4), rheumatoid nodules (criterion 5), serum rheumatoid factor (criterion 6) and radiographic change (criterion 7) [22]. These ACR criteria were determined as the follows. The criterion 1 was determined by answers to the questions "Have you ever had stiffness in your hands when first getting out of bed in the morning on most days for at least 6 weeks?" and "How long after getting up and moving around does the morning stiffness last?" The criterion 2 was determined from examination variables documenting the presence of soft tissue swelling in 3 or more of the following 10 joint areas: right or left proximal interphalangeal joint (PIP), metacarpophalangeal joint (MCP), wrist, knee, and first metatarsophalangeal joint (MTP). Data indicating the presence of joint swelling were available for 4 PIP joints and 5 MCP joints bilaterally. Swelling was classified as present in each joint area if it was found in 1 or more of the individual joints in these areas. The criterion 3 was determined from examination variables documenting the presence of soft tissue swelling in at least 1 right or left PIP, MCP, or wrist joint area. The criterion 4 was determined from examination variables documenting the presence of soft tissue swelling of the same joint areas on both sides of the body simultaneously (right and left PIP, MCP, wrist, knee, and first MTP joints). The criterion 5 was determined from the examination variable documenting the presence of subcutaneous nodules observed on the shaft of the right forearm, the left forearm, or both forearms. The criterion 6 was determined from blood samples using the Singer–Plotz latex agglutination test. For the purposes of this study, all non-zero, non-missing values were classified as being RF positive. The value of the lowest RF titer was 1:20. The criterion 7 was determined from radiographs of the hands and wrists.

The NHANES III included 837 participants who were at least 20 years old with RA, whereas participants who were with missing serum lycopene ($n = 143$) was excluded, yielding a sample of 694 RA participants (232 men and 464 women) for this study (see Fig. 1).

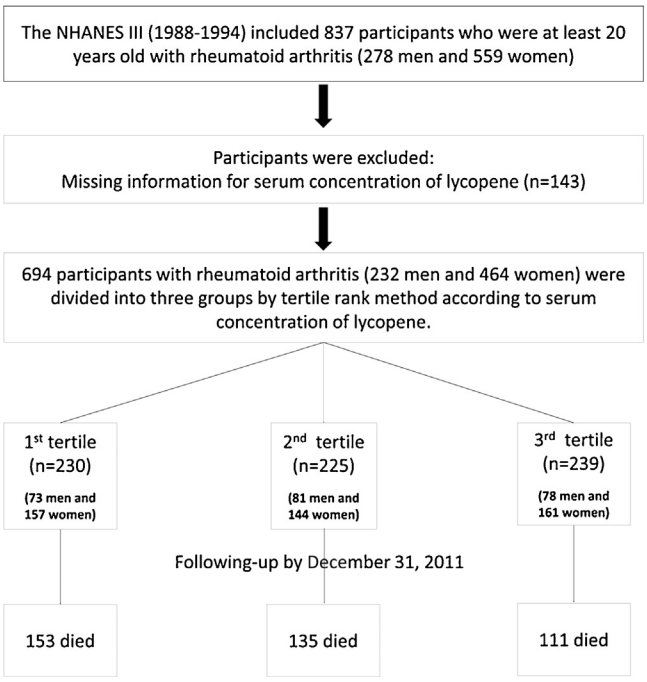

Fig. 1. Diagram of the study design.

2.2. Assessment of exposure

For laboratory serum measurement, blood was collected at interview (1988–1994) by venipuncture in the mobile examination clinics (MEC) according to the standard protocol. Serum was separated by centrifugation after samples were kept at room temperature for 30–60 min. Serum was frozen at −20 °C and transported on dry ice to the CDC laboratory. Serum concentrations of lycopene (μmol/L) were measured using high-performance liquid chromatography with multi-wavelength photodiode-array absorbance detection.

2.3. Mortality follow-up

Although the NHANES III is a cross-sectional study, the National Center for Health Statistics created an NHANES III Linked Mortality File provides mortality follow-up data from the date of NHANES III interview (1988-1994) through December 31, 2011. The method of probabilistic matching was used to link NHANES III participants with the National Death Index to ascertain vital status and cause of death. Of the 694 RA participants aged 20 years and older, 399 (57.5%) died by December 31, 2011.

2.4. Assessment of co-variables

Study covariates included race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American and other), gender (male and female), age group (20–39, 40–59 and 60 years and older), body mass index (BMI < 25 and BMI ≥ 25), smoking status (no smoker, past smoker and current smoker), physical activity (yes and no), disease activity (number of pain joint, number of swelling joint, C-reaction Protein), prescription medicine use and common chronic disease conditions included hypertension, diabetes, heart attack, stroke, cancer, bronchitis, emphysema, liver function and estimated glomerular filtration rate (GFR) calculated by using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation, as previously described [23].

2.5. Statistical analysis

All statistical analyses in this study were performed using SAS Procedures (SAS version 9.3, SAS Institute, Cary, NC, USA). Continuous variables were presented as means with standard