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Plasma carotenoid levels as biomarkers of dietary carotenoid consumption: A systematic review of the validation studies

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ABSTRACT

Background: Previous research has demonstrated that plasma carotenoids are a reliable biomarker of usual fruit and vegetable intake. The review aims were to synthesize (i) the mean dietary intake and (ii) plasma concentrations of carotenoids reported from validation studies (iii) compare the strength of the relationship between the two, measured using different dietary assessment methods.
Methods: Six databases were used to locate studies that included: adult populations, assessment of dietary intake, measurement of plasma carotenoids and reported the comparison between the two measures.
Results: One hundred and forty-two studies were included with 95,480 participants, the majority of studies were cross-sectional (n = 86), with randomized controlled trials (RCTs) (n = 18), 14 case–control studies and 13 cohorts. The most common reported dietary carotenoid and plasma carotenoid was lycopene: weighted dietary mean intake (4555.4 ug/day), and plasma concentration 0.62 umol/L (95% CI: 0.61, 0.63, n = 56studies. The strongest weighted correlation between the two measures was found for cryptoxanthin (r = 0.38, 95% CI 0.34, 0.42) followed by a-carotene (r = 0.34, 95% CI 0.31, 0.37).
Conclusion: This review summarizes typical dietary intakes and plasma concentrations and their expected associations based on validation studies conducted to date which provides a benchmark for future validation studies.

1. Introduction

Epidemiological studies have reported that regular consumption of fruits and vegetables, in accordance with World Cancer Research Fund guidelines [1], is associated with reduced risk of some cancers including breast, oesophageal and lung [2–6]. In addition having an adequate fruit and vegetable intake substantially lowers risks of coronary heart disease [7,8], stroke [9,10] and type 2 diabetes mellitus [11,12] specifically showing decreased risk with higher consumption of green leafy vegetables [13,14]. In addition fruit and vegetable intake has been associated with decreased risk of asthma in adults and children [15].

A variety of plant components such as fiber, carotenoids and other phytochemicals are thought to contribute to these protective effects [16]. Carotenoids are obtained from the diet as brightly coloured pigments which originate in plant foods. Variations in digestion and absorption exist between individuals, with plasma concentrations of carotenoids having a half-life between 26 and 76 days [17]. However some carotenoid supplement studies report peak concentrations in plasma up to two weeks following consumption [18].

The main carotenoids of interest are lycopene and β-carotene and this is because of the documented associations with decreased risk of disease. These carotenoids are highly prevalent in fruits and vegetables. Specifically lycopene is found in tomatoes and tomato based products while β-carotene is found in high concentrations in carrots and cantaloupe. Other carotenoids including cryptoxanthin are found in fruits such as oranges, while lutein is found in lettuce, kale and spinach [19]. Lutein is often combined with zeaxanthtin in reports due to chromatographic overlap.

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Accurate assessment of fruit and vegetable intakes is fundamental to a range of research domains, including epidemiological studies examining the relationship between dietary intake and disease outcomes, evaluating whether populations are consuming adequate intakes of fruit and vegetables and hence obtaining the protective advantage from disease and monitoring of changes in population intakes over time. Measuring the dietary intake of carotenoids and examining the relationship with plasma carotenoid concentrations is one way in which intake can be scrutinized using an independent biomarker and the validity of intake assessment method evaluated.

Validity is defined as the accuracy of a measure, assessed by comparing results from an assumed "gold standard" measure of known validity such as doubly labelled water, to values obtained by another instrument. In free living individuals, there is no gold standard measure of total or individual nutrient intakes when comparing actual intake with that measured using a dietary assessment method or tool [20]. However, comparison of one dietary intake assessment method to another method is a common approach, but does carry the risk of correlated errors [21,22]. Plasma biomarkers offer an objective and independent variable that can act as a proxy for intake of specific foods and therefore is suitable for use when validating dietary assessment tools [23]. Regardless of individual variability in absorption, availability, and metabolism [24,25], plasma concentrations of carotenoids reflect intake of fruits and vegetables due to their abundance in these foods [24]. Due to the diverse phytochemical composition across a range of vegetables and fruits, selecting a single carotenoid as sole biomarker is not likely to be meaningful [26]. Instead, a range of carotenoids is recommended when using them as biomarkers of fruit and vegetable intake. Previous research has shown a dose–response relationship between intake and appearance of carotenoids in plasma [27], making carotenoids a fairly reliable biomarker of total carotenoid intake However, the strength of the relationship between intake of individual dietary carotenoids and plasma concentrations across a range of studies has not been ascertained. Establishing reference ranges for diet and plasma carotenoids, could allow comparison of specific dietary tools in terms of validity statistics in measuring dietary intakes of carotenoids and/or fruits and vegetables.

Therefore the aims of this review were to synthesize from the best available dietary validation studies to date (i) the mean dietary intake of carotenoids in adults; (ii) the mean plasma carotenoid concentrations reported in dietary validation studies (iii) the strength of the relationship between dietary intakes of carotenoids, measured using different dietary intake assessment methods, and plasma carotenoid concentrations.

2. Methods

A three-step strategy was undertaken to identify studies published in the English language up to May 2014. The review methodology was registered with PROSPERO (ID number CRD42013004777).

In stage one, six online databases were searched, CINAHL, Cochrane, MEDLINE, ProQuest, PubMed and Excerpta Medica. Key words used individually and in combination were: dietary assessment OR food frequency questionnaire OR diet/dietary recall, diet record, weighed food record, validity/validation AND carotene OR carotenoids OR fruit OR vegetable. Electronic searches were supplemented by manual cross checking of the reference lists of relevant publications. All study designs were included.

After the removal of duplicates, stage 2 involved the assessment of titles and abstracts of identified studies by two independent reviewers with discrepancies decided by consensus using a third reviewer. *A'priori* inclusion/exclusion criteria were applied to determine the eligibility of each publication for inclusion in the review, as per the following inclusion criteria: adult populations ($\geq$18 or 19 $\geq$ yrs or 'adults' depending on the database searched), a measure of dietary intake, a measure of plasma carotenoids as a biomarker of intake, reported the comparison/correlation/agreement between diet and biomarker assessments. Carotenoids, individually or in combination, included α- and β-carotene, cryptoxanthin, lycopene, zeaxanthin, and lutein. Papers that met the inclusion criteria, or where eligibility was unclear, were retrieved. These were then evaluated for inclusion by two independent reviewers with discrepancies discussed with a third person.

Risk of bias was assessed using a standardized tool from the American Academy of Nutrition and Dietetics [28]. Ten quality criteria were rated as being absent, present or unclear in each study. This included the assessment of population bias, study blinding, a description of the intervention and assessment tool, statistical methods, and study funding. An overall quality rating was assigned to each study as being plus/positive, neutral or minus/negative.

Data were extracted using standardized tables developed for this review. In cases of uncertainty regarding quality assessment, or data extraction, a third independent reviewer was consulted until consensus was reached.

The dietary intakes of carotenoids and plasma carotenoid concentrations, and the relationship between them, were grouped by dietary assessment method where possible. These dietary intake assessment methods were 24 h recall, food frequency questionnaire (FFQ), diet history, food records, and other non-standard dietary questionnaires which included dietary methods not covered by the other categories.

2.1. Data synthesis

Results were pooled using meta-analysis if the following data were available in addition to the reported number of participants: correlation coefficients (or equivalent) between dietary carotenoid intake and plasma carotenoid concentrations (α carotene, β carotene, cryptoxanthin, lutein/zeaxanthin and lycopene); dietary intakes (reported as μg/day) and plasma concentrations. For plasma concentrations the data were entered as μmol/L and if reported in other units they were converted to μmol/L using the relevant conversion factors. If there was significant heterogeneity, the random effects model was used for statistical analysis. If studies reported more than one correlation statistic between diet and plasma due to use of multiple dietary assessment methods, the strongest correlation was used (n = 3 studies).

Analysis were undertaken by each individual carotenoid and also separately for each diet assessment method (24 h recall, FFQ, diet history, food record and questionnaire) and where possible, overall regardless of diet assessment method. Sub-analysis by sex was also undertaken if there were enough studies to conduct separate meta-analyses. The reporting of the associations between diet and plasma carotenoid concentrations was rarely separated out by supplement use versus no use, supplements were most often added into dietary intake estimates thus the impact of supplements could not be compared in this review.

There were not enough studies for comparison by ethnicity. Meta-analyses were conducted using Comprehensive Meta-Analysis Professional version 2 (Englewood, New Jersey, USA).

3. Results

The search strategy identified 4176 articles, as outlined in Fig. 1. For the full search strategy see Supp Table 1. Following elimination of duplicates, initial assessment of titles and abstracts, and