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Total Antioxidant Capacity in beta-thalassemia: A systematic review and meta-analysis of case-control studies

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ABSTRACT

Total Antioxidant Capacity (TAC), a biomarker measuring the antioxidant potential of body fluids, including redox synergistic interactions, is influenced by the presence of products of catabolism such as bilirubin (BR) and uric acid (UA). Hyperuricaemia and increased BR levels were observed in thalassemia. In order to evaluate the differences in TAC values between thalassemic patients and healthy subjects, we performed a systematic review and meta-analysis of case-control studies. After the exclusion of data deemed unsuitable for meta-analysis inclusion and a study imputed of bias by Trim-and-fill analysis, mean difference (MD) and confidence intervals 95% (CI 95%) were calculated by the random effect model for beta-thalassemia major (BTM) (1351 subjects: 770 thalassemic and 581 controls, from 15 studies) and Trait (BTT) or Hemoglobin E (BTE) (475 subjects: 165 thalassemic and 310 controls, from 5 studies). Despite the differences in clinical symptoms and severity, similar decreased levels of TAC were found in BTM [MD −0.22 (−0.35 −0.09) $p < 0.001$] and BTT or BTE [MD −0.22 (−0.44 −0.01) $p < 0.05$]. In conclusion, UA and BR interference on TAC suggests that corrected TAC and in particular the UA-independent TAC, considering the prominent influence of UA, might be the better approach to evaluate body antioxidant status.

1. Introduction

Beta-thalassemia major (BTM) is the most prevalent type of beta-thalassemia (BT), comprising also thalassemia Trait (BTT or minor), thalassemia Intermedia (BTI) and Hemoglobin E thalassemia (BTE) (Rund and Rachmilewitz, 2005). BTM requires

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regular transfusion therapy to maintain hemoglobin levels of at least 9–10 g per deciliter and to reduce hepatosplenomegaly due to extramedullary hematopoiesis (Rund and Rachmilewitz, 2005). Both haemolysis and transfusional iron overload cause excessive generation of free radicals (through the Fenton reaction), and, consequently, iron-chelation therapy is largely responsible for doubling the life expectancy of patients with BTM (Rund and Rachmilewitz, 2005). Excessive generation of free radicals can cause oxidative damage to biological macromolecules such as DNA, lipids, carbohydrates and proteins (Halliwell and Gutteridge, 1984). In beta-thalassemia, malonyldialdehyde (MDA; a by-product of lipid peroxidation) levels correlate positively with serum iron and oxidative stress levels were shown to largely normalize in response to oral therapy with antioxidants (Rund and Rachmilewitz, 2005). Oxidative stress is the imbalance between reactive oxygen species (ROS) and antioxidant defense (Halliwell and Cross, 1994). ROS is a collective term used by biologists to include not only oxygen-derived radicals, such as the superoxide anion, hydroxyl radical, peroxyl, alkoxyl and oxides of nitrogen, but also some derivatives of oxygen that do not contain unpaired electrons, such as the hydrogen peroxide and the hypochlorous acid produced by inflammatory cells (Halliwell and Cross, 1994). The human body has a complex strategy for countermanding the deleterious effects of ROS, which include both antioxidative and repair mechanisms (Serafini et al., 2011). Antioxidant defenses of the body are composed of enzymes, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) and low molecular weight antioxidants, including glutathione (GSH), uric acid (UA), bilirubin (BR), thiols (SH), vitamin E (Vit. E), ascorbic acid (Vit. C), carotenoids and other nutritional antioxidants (Serafini et al., 2011).

Synergistic interactions between antioxidants, in part involving antioxidant regeneration, need to be taken into account in order to properly assess antioxidant status in vivo. Total Antioxidant Capacity (TAC), defined as the moles of oxidants neutralized by one litre of plasma (Niki, 2010), is a biomarker measuring the antioxidant potential of body fluids, including redox synergistic interactions (Niki, 2010).

Over the past decade, a large number of assays and kits for the measurement of TAC in biological matrices have been developed and the most commonly used assays, their basic features, and their points of strength and weakness, have been extensively discussed in several comprehensive reviews (Bartosz, 2010; Knasmüller et al., 2008; Pinchuk Shoval et al., 2012; Dilis and Trichopoulou, 2010).

The more commonly used methods are the Ferric Reducing Antioxidant Potential (FRAP) and the Trolox Equivalent Antioxidant Capacity (TEAC) within the single electron transfer (SET)-based assays and the Total-radical Trapping Antioxidant Parameter (TRAP) and the Oxygen Radical Antioxidant Capacity (ORAC) within the hydrogen atom transfer (HAT)-based methods (Serafini et al., 2011; Bartosz, 2010; Knasmüller et al., 2008; Pinchuk Shoval et al., 2012; Dilis and Trichopoulou, 2010). Although the discussion on the method used for determining TAC is not a central issue in the current study, it must be stated that the results obtained from FRAP and ORAC measurements correlate well, but not between the aforementioned methods and TEAC (Cao and Prior, 1998). On the other hand, the copper(II) reduction assay (CUPRAC) does significantly correlate with FRAP and TEAC, but not with the 1,1-diphenyl-2-picrylhydrazyl assay (DPPH) for plasma samples (Campos et al., 2009). Despite the different features of the TAC methods, their common major bias is that they are influenced by the presence of products of catabolism, such as bilirubin (BR) and uric acid (UA) (Cao and Prior, 1998). Both hyperuricaemia (Ricchi et al., 2012) and increased BR levels (Dhaliwal et al., 2004) can be observed in thalassemia.

The objective of this meta-analysis was to evaluate the differences in TAC values between thalassemic patients and healthy subjects. To this aim, a systematic review of the available literature and meta-analysis of included case-control studies was conducted in this work.

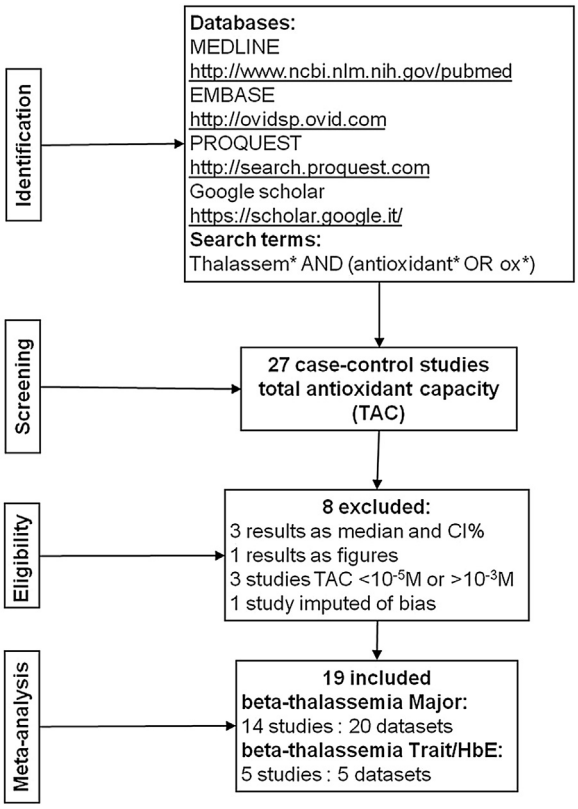

Fig. 1. Four-phase flow diagram of systematic review and meta-analysis.

2. Methods

2.1. Literature screening

We performed a systematic search in the MEDLINE, EMBASE, ProQuest and Google scholar databases for relevant literature up to September 2015 with the search string: [thalassem* AND (antioxidant* OR ox*)]. The flowchart outlining the process of search criteria and study selection is shown in Fig. 1.

2.2. Study selection

Studies that met the following criteria were included for meta-analysis: (1) The outcome had to be thalassemia; (2) at least two comparison groups (case vs. control group); (3) studies in which the plasma TAC levels were expressed as millimolar (mM). Exclusion criteria included: (1) Review articles; (2) in vitro studies; (3) animal models; (4) patients with other diseases. Trials were initially identified through title or abstract. Study selection was performed independently by two reviewers (H.M. and M.P.) to ensure uniformity. Discrepancies were resolved by discussion with a third reviewer (I.P.).

2.3. Data extraction

The data extracted from each study included the first-author's name, year of publication, country of the study performed, ethnicity, subject characteristics, type of BT, comorbidities, method of evaluation of TAC and other markers of plasma redox status. For each study with more than one beta-thalassemic group, we