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Review article

Changes in cerebral metabolites in type 2 diabetes mellitus: A meta-analysis of proton magnetic resonance spectroscopy

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ABSTRACT

To investigate whether there were differences and consistent patterns that highlight and consolidate the metabolite changes in type 2 diabetes mellitus (T2DM), a meta-analysis of proton magnetic resonance spectroscopy (MRS) was conducted. PubMed, Web of Science, and Embase databases were searched up to August 2016 for collecting the relevant studies. After an inclusion and exclusion criteria, the data was extracted. The data was analyzed using Stata software v.12.0. The weight mean difference (MD) and 95% confidence interval (CI) were used to compare continuous variables. A total of 10 studies (with a total of 244 T2DM patients and 223 healthy controls) were included. N-Acetyl Aspartate (NAA)/creatine (Cr) levels were decreased in the frontal lobe (MD = −0.20, 95%CI = −0.33 to −0.06, P = 0.005) and lenticular nucleus (MD = −0.14, 95%CI = −0.22 to −0.06, P = 0.001); choline (Cho)/Cr levels were increased in the lenticular nucleus (MD = 0.15, 95%CI = 0.02–0.28, P = 0.025); myo-inositol (MI)/Cr levels were increased in the in the occipital lobe (MD = 0.11, 95%CI = 0.02–0.19, P = 0.017) and parietal lobe (MD = 0.16, 95%CI = 0.05–0.28, P = 0.006); MI levels were increased in the frontal white matter (MD = 0.52, 95%CI = 0.14–0.90, P = 0.008). The results of our meta-analysis indicated that metabolite levels were altered in different regions of brain, which may be shown with MRS and caused clinical symptoms in T2DM further.

1. Introduction

Diabetes is an important cause of mortality, morbidity, and health-system costs in the world [1]. According to a recent article, from 1980 to 2014, worldwide age-standardized adult diabetes prevalence increased from 4.3% to 9.0% in men and from 5.0% to 7.9% in women, the number of adults with diabetes in the world increased from 108 million in 1980 to 422 million in 2014 [2]. Type 2 diabetes mellitus (T2DM) might be a risk factor for mild cognitive impairment progressing to Alzheimer's disease (AD) [3]. Several structural and functional neuroimaging findings have shown visible alterations in numerous brain regions of patients with T2DM, and these changes may result in cognitive impairment [4–6]. However, only magnetic resonance spectroscopy (MRS) provided more detail regarding metabolite changes in the brain that might be related to functional and structural alterations.

^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive neuroimaging technique that evaluates specific chemical metabolite measures in vivo [7]. The metabolite concentrations commonly detected and studied in the cerebral area using MRS include those of N-Acetyl Aspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (MI), glutamate and glutamine (Glx), and gamma-aminobutyric acid (GABA). NAA is considered as a marker of neuronal viability and mitochondrial energy metabolism [8]. Changes in Cho levels indicate destruction of the cell membrane or myelin sheath [9]. Cr is highly concentrated in muscle and brain tissues, in which Cr also appears to act in osmoregulation and neurotransmission [10]. Myo-inositol plays a role in the second messenger system [11]. Glx, key amino acids in the cerebral area, the peak can be resolved into individual wavelets in high-field MRI [12]. GABA plays a significant role within the pain processing pathways of the central nervous system [13].

In recent decades, a number of MRS studies in T2DM using different methods have revealed that the profiles of metabolite changes in diverse cerebral regions are different between T2DM patients and healthy controls, but inconsistent findings with results. To our knowledge, a meta-analysis of ^{1}H-MRS studies in people with T2DM has never been reported previously. To investigate whether there were differences and consistent pattern that highlight and consolidate the metabolite changes in T2DM, a meta-analysis was conducted.

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2. Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, we made a predefined protocol of objectives, retrieval strategies, inclusion and exclusion criteria, result measurements and statistics analysis methods [14,15].

2.1. Data sources and search

A systematic search was performed using the electronic databases of Web of Science, PubMed and Embase, and the search terms were as follows: "type 2 diabetes mellitus"[Mesh], "T2DM", "type 2 diabetes", "diabetes mellitus", "diabetes" "diabetic", "Magnetic Resonance Spectroscopy"[Mesh], "magnetic resonance spectroscopy", "MR spectroscopy", and "MRS". The cut-off date was August 1, 2016. A manual search was also performed through references of reviews, previous systematic reviews and key articles. All potential eligible trials were considered for review.

2.2. Inclusion and exclusion criteria

Studies were included if they (1) written in English and full text could be obtained, (2) performed proton MRS comparing T2DM subjects and healthy controls (HC), and (3) reported at least a single metabolite ratio or concentration. Studies were excluded if they (1) were not written in English or if they were meeting abstracts or nonclinical studies, (2) did not use a HC group or the T2DM group, (3) included subjects who had other co-morbidities such as neurological or psychiatric disease, head trauma, liver or kidney dysfunction, alcohol or drug abuse, and (4) did not provide a date, even after corresponding with the author(s).

2.3. Data extraction

Two authors searched and screened the titles, abstracts and full-text articles independently, then extracted relevant information from each eligible study using a standardized form. For each of the included studies, the first author, year of publication, number of participants, brain areas reported, types of MRS measurements (absolute measure or ratio), strength of the magnetic field (Tesla), echo time (TE), repetition time (TR), and results of the studies were recorded. If there were disagreements about article selection, they were resolved through discussion by all authors.

2.4. Statistical analysis

The data was analyzed using Stata software v.12.0 (Stata Corporation, College Station, TX, USA). Weight mean differences (MD) and 95% confidence interval (95% CI) were used to analyze continuous data. For the WMDs calculation, the standard deviation individual was used. The inconsistency index (I-squared, I^2) was used to examine between-study heterogeneity. If $I^2 > 50\%$ the heterogeneity was unacceptable then the data was analyzed using a random-effects model. If $I^2 < 50\%$ the heterogeneity was acceptable then the data was analyzed with a fixed-effects model. A sensitivity analysis was performed to test the reliability of the results of significant findings in a cyclic manner such that we removed a single study at a time and then repeated the analysis. If the results did not change significantly before and after the removal of one study at a time, then the results were considered stable.

3. Results

3.1. Study identification and selection

The search retrieved 3360 studies and 1771 papers were initially removed due to duplication, 1525 were excluded based on title and abstracts. Of the 58 reports assessed for full text analysis, and 10 [16–25] (with a total of 244 T2DM patients and 223 healthy controls) fulfilled the inclusion criteria (Fig. 1). Demographic and clinical characteristics and technique details of the studies were included in Table 1.

3.2. NAA/Cr, Cho/Cr, NAA/Cho, MI/Cr

Compared with HC, the meta-analysis showed a significantly decreased NAA/Cr levels in the frontal lobe ($I^2 = 0\%$, MD = −0.20, 95%CI = −0.33 to −0.06, P = 0.005) and lenticular nucleus ($I^2 = 0\%$, MD = −0.14, 95%CI = −0.22 to −0.06, P = 0.001) [16,18,19,21–23,25]; the NAA/Cr level in the occipital lobe, thalamus and parietal lobe had no significant difference (Table. 2).

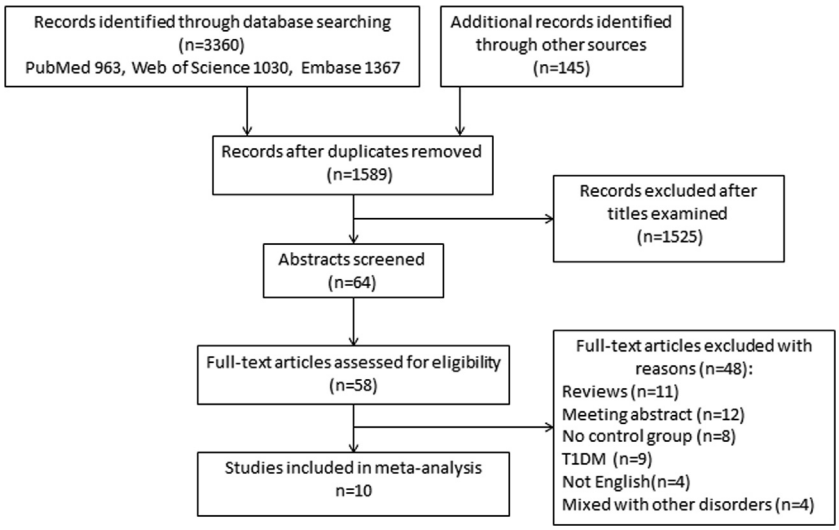

Fig. 1. Flow chart of article selection.

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