EFFECT OF BRANCHED CHAIN AMINO ACIDS ON PREDIABETIC PATIENTS : A SYSTEMATIC REVIEW & META-ANALYSIS OF PROSPECTIVE STUDIES

Biochemistry

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ABSTRACT

Background- Published findings suggest that branched-chain amino acids (BCAAs), are associated with insulin resistance and type 2 diabetes. Other amino acids such as aromatic amino acids, glycine, glutamine, and glutamate have also been related to prediabetes and type 2 diabetes risk.
Objectives- To conduct a systematic review of prospective studies for evaluating effect of BCAAs on prediabetes.
Methodology- We searched PUBMED, MEDLINE and EMBASE databases through November2017. We conducted meta-analysesof Prospective studies of BCAAs, with data estimates from at least 8 prospective studies and type 2 diabetes risk were conducted, and multivariable- adjusted relative risks of type 2 diabetes were calculated per study-specific SD difference in a given metabolite.
Results- We identified 19 prospective studies reporting associations of BCAAs and prediabetes& type 2 diabetes. We found 36% higher risk of type 2 diabetes per study-specific SD difference for iso-leucine (pooled relative risk 1.36 [1.24–1.48]; $I^2 = 9.5\%$), 36% for leucine (1.36 [1.17–1.58]; $I^2 = 37.4\%$), 35% for valine (1.35 [1.19–1.53]; $I^2 = 45.8\%$), 36% for tyrosine (1.36 [1.19–1.55]; $I^2 = 51.6\%$), and 26% for phenylalanine (1.26 [1.10– 1.44]; $I^2 = 56\%$).
Conclusion- Our results confirmed that, several branched chain amino acids are consistently associated with the risk of developing type 2 diabetes in prediabetic patients.

INTRODUCTION

Type 2 diabetes is among the most prevalent chronic diseases, affecting more than 380 million people worldwide in 2014 (1). Risk factors for type 2 diabetes consist of a combination of unhealthy diet, lifestyle, and genetic factors that may interact with each other and with the environment (2). In the last decade, high throughput metabolomics technologies have provided insights into the pathophysiological pathways and understanding of the disease and its precedents (3). To date, published findings suggest that branched chain amino acids (BCAAs) are associated with insulin resistance and type 2 diabetes (4). Other amino acids such as aromatic amino acids, glycine, glutamine, and glutamate have also been related to prediabetes and type 2 diabetes risk (5–7). We hypothesized that elevated concentrations of some metabolites, such as BCAAs and aromatic amino acids, would be associated with a higher risk of prediabetes and type 2 diabetes, while other metabolites (e.g., glycine and glutamine) would be inversely associated. We conducted a systematic review of human studies for specific metabolite markers of type 2 diabetes risk: BCAAs (isoleucine, leucine, and valine), aromatic amino acids (tyrosine and phenylalanine), glycine, glutamine, alanine, and histidine. The rationale behind performing this meta-analysis was to assess the effect of branched chain amino acids on pre-diabetic patients.

LITERATURE SEARCH

We conducted a systematic search of published literature in three different databases PUBMED, MEDLINE and EMBASE through November 2017, and hand searched reference lists of articles and key journals for human studies evaluating effect of branched chain amino acids on prediabetic patients.

Inclusion criteria : We have included studies in which prediabetes and type 2 diabetes were defined as impaired glucose tolerance, impaired fasting glucose. according to standard criteria for diagnosis and classification of diabetes (1,10) (e.g., impaired fasting glucose defined as fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] and type 2 diabetes defined as fasting glucose $126 mg/dL [7.0 mmol/L] or other criterion justified ranges).

Exclusion criteria : We excluded animal studies; studies conducted in

children, adolescents, and pregnant women; studies of type 1 diabetes or gestational diabetes mellitus; non original papers (reviews, commentaries, editorials, or letters); and duplicate publications.

DATA EXTRACTION-

Following information has been extracted: authors, year of publication, study name and design, sample size, participant characteristics, duration of follow-up (if applicable), analytic technique, biological sample, primary and secondary outcomes measured, statistical tests, confounding factors, whether the analyses were corrected for multiple comparisons, and major findings (analyzed metabolites, adjusted relative risks [RRs] or odds ratios [Ors]).
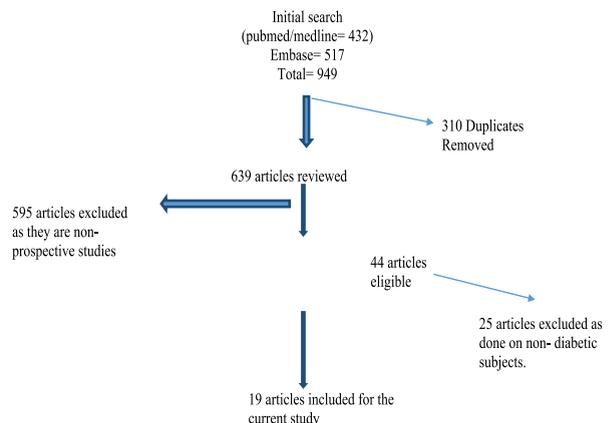
STUDY SELECTION-

Figure shows the results of the literature search and study selection. Among the 949 unique abstracts reviewed in- dependently and in duplicate by two investigators, 905 were excluded. Among the 44 full text articles reviewed thereafter, 25 were excluded. After final exclusions, and with addition of 8 references identified by hand searching of citations, 19 publications met the inclusion criteria and were included in the present systematic review (5-23).

RESULTS
Table 1- Characteristics of study selected

Study	Year	Duration	Metabolite	HbA1c (%)
Nicholson et al	2011	4 years	Isoleucine	7.2
Wang TJ et al	2011	3 years	Isoleucine	6.4
Floegel et al	2011	1 year	Isoleucine	6.3
Padberg et al	2012	6 weeks	Isoleucine	6.3
Rhee et al	2012	2 weeks	Isoleucine	6.6
Stanco et al	2012	2 months	Isoleucine	6.7
Ferrannini et al	2012	3 years	Leucine	6.3
Wang Sutler et al	2008	2 years	Leucine	6.1
Chang et al	2011	6 weeks	Leucine	7.2
Palmer et al	2010	1 year	Leucine	7.1
Tillin	2010	3 months	Leucine	7.4
Krebs M et al	2013	2 years	Valine	6.4
Ley SH	2012	2 years	Valine	6.2
Cornelis et al	2011	1 years	Valine	6.6
Shah SH et al	2010	3 months	Valine	7.2
Wurtz P	2008	3 years	Valine	7.0
Mahendran et al	2007	2 years	Valine	7.4
Drogan et al	2004	1 year	Valine	6.2

Table 1 shows the studies included as seen total 18 studies (5-22) which were prospective in nature in which 5 studies are for isoleucine, 6 for leucine and 7 for valine. HbA1c for each study is also mentioned the mean HbA1c for isoleucine was 6.4, for leucine 6.2 and 7.2 for valine.

Meta Analysis of BCAAs- Nine studies examining the prospective association between several amino acids and pre-diabetes/ type 2 diabetes were included in meta analyses (5-22). Figure 2 shows the pooled RR for incident of prediabtes and type 2 diabetes per study-specific SD difference in the amino acid analyzed. The pooled RRs for incident type 2 diabetes per study-specific SD difference in the BCAAs isoleucine, leucine, and valine were 1.36 (95% CI 1.24–1.48), 1.36 (1.17– 1.58), and 1.35 (1.19–1.53), respectively, with no significant evidence of between- study heterogeneity for isoleucine and leucine (I^2 = 9.5%, P for heterogeneity = 0.36, and I^2 = 37.4%, P for heterogeneity = 0.172, respectively) and moderate heterogeneity for valine (I^2 = 45.8%; P for heterogeneity = 0.086).

METABOLITE		RR (95% CI)	N studies	I^2
BCAA				
Isoleucine		1.36 (1.24-1.48)	6	9.5%
Leucine		1.36 (1.17-1.58)	5	37.4%
Valine		1.35 (1.19-1.53)	7	45.8%

DISCUSSION AND CONCLUSIONS
This systematic review and these meta- analyses identified a number of branched chain amino acids prospectively associated with prediabetes and type 2 diabetes in humans. Current evidence suggests that amino acid (BCAAs) metabolites not only are altered in individuals with type 2 diabetes but also exhibit significant prospective associations with prediabetes and/or type 2 diabetes. Our results from prospective studies support robust positive associations of BCAAs (leucine, isoleucine and valine) with incident type 2 diabetes. The present meta-analyses provide the most comprehensive analysis to date of the associations between BCAAs and the risk of type 2 diabetes. These results suggest that alterations in blood BCAAs may be useful in identifying novel bio- markers of type 2 diabetes. amino acids may directly promote insulin resistance, possibly via disruption of insulin signalling in skeletal muscle (5-21); there could also be a decreased uptake and increased release of BCAAs from skeletal muscle due to increased protein catabolism in insulin resistance (12).

Furthermore, BCAAs can modulate insulin secretion (23) and promote diabetes via hyperinsulinemia, leading to pancreatic b-cell exhaustion (5). Together, current evidence suggests that elevations of blood BCAAs may be early signals of deterioration of glycemic control and insulin sensitivity. Since lifestyle and dietary interventions have a great impact on type 2 diabetes prevention (22), future studies should focus on metabolic biomarkers that can modulate the effects of dietary intake, and vice versa, and their relation to insulin resistance and diabetes. In addition, certain biomarkers are directly derived from the digestion and gut absorption of food constituents; therefore, future studies relating metabolites derived from gut microbiota and type 2 diabetes may be of interest. The applications of these new approaches will contribute to future progress in the field of molecular nutritional epidemiology (23). Taken together, the present systematic review provides evidence that several metabolites, including BCAAs are associated with the risk of prediabetes and type 2 diabetes. Our data indicate that the BCAAs isoleucine, leucine, and valine are positively associated with the risk of type 2 diabetes.

CONFLICT OF INTEREST
None declared

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