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Article

The Biochemical Expression of Branched Chain Amino Acid in Predicting the Glucose Intolerance among Individuals with Various Glycemic Status–A Prospective Observational Study

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Abstract: ***Background:*** *Branched-chain amino acids (BCAAs) are potential biomarkers in glucose metabolism and insulin resistance. Different levels of BCAAs have been associated with glucose intolerance and Type 2 diabetes mellitus (T2DM). However, their role in predicting glucose intolerance among individuals with various glycemic grades remains underexplored.* ***Aim:*** *To investigate the biochemical expression of BCAAs in predicting glucose intolerance among individuals with impaired glycemic tolerance, newly diagnosed T2DM, and long-term T2DM patients (more than 5 years of duration).* ***Methods:*** *This prospective observational study was conducted at a Tertiary Care Centre at Puducherry from November 2023 to February 2024. A total of 90 participants were divided into three groups: Group 1 (prediabetics, n=30), Group 2 (newly diagnosed T2DM, n=30), and Group 3 (T2DM patients with more than 5 years duration, n=30). Convenient sampling was used to select the participants. BCAA levels were estimated and correlated with anthropometric parameters (Body Mass Index) and biochemical markers (fasting glucose, postprandial glucose, and HbA1c). Inclusion criteria involved impaired fasting glucose and glucose tolerance, with a minimum IDRS score of >30. Exclusion criteria included pregnant women, critically ill patients, and those with IDRS scores <30.* ***Results:*** *BCAA levels showed significant differences among the three groups, with the highest levels observed in newly diagnosed T2DM patients. Correlations were found between BCAA levels and anthropometric (BMI) and biochemical parameters (fasting and postprandial blood glucose, HbA1c), suggesting a strong association between BCAA levels and glucose intolerance. The findings highlight the potential role of BCAAs as an early marker for glucose dysregulation in prediabetics and newly diagnosed T2DM individuals.* ***Conclusion:*** *BCAAs may serve as valuable biomarkers in the prediction of glucose intolerance across different glycemic statuses, providing insight into early-stage metabolic disturbances that precede the development of T2DM. Further studies with larger sample sizes and diverse populations are defensible to confirm the clinical relevance of BCAAs in diabetes management and prevention.*

Keywords: Branched-chain amino acids, glucose intolerance, biochemical markers, glycemic statuses Diabete.

INTRODUCTION

Nearly 450 million people worldwide suffer with diabetes. In poorer nations, this rise in prevalence is particularly noticeable (1). In India, diabetes mellitus (DM) with a complex etiology—including lifestyle and genetic factors—is more prevalent. In India, 74 million individuals have been diagnosed with this epidemic, which is spreading quickly (2).

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This elevated prevalence is the result of prediabetes, which is defined by impaired glucose tolerance and impaired fasting glucose (3). These people have blood glucose levels that are higher than usual but still below the cutoff point for diabetes. There is serious concern about the spread of disease to economically disadvantaged groups in society, which calls for immediate preventive action (4). The Chennai Urban Rural Epidemiology Study's [CURES] multiple logistic regression analysis results served as the foundation for the creation of the Indian Diabetes Risk Score [IDRS]. IDRS used four risk factors: age, abdominal obesity, family history of diabetes and physical activity. An IDRS value > or = 60 had the optimum sensitivity (72.5%) and specificity (60.1%) for determining undiagnosed diabetes with a positive predictive value of 17.0%, negative predictive value of 95.1%, and accuracy of 61.3%.This simplified Indian Diabetes Risk Score is useful for identifying undiagnosed diabetic subjects in India and could make screening programmes more cost effective (5). Metabolomics which is evolved recently deals with the metabolic dynamics that reflects the response of living system to pathophysiological stimuli and genetic modifications if any and the surrounding environment (6). Numerous investigations have found that type 2 diabetes mellitus is linked to biomarkers of underlying pathways, which are tiny circulating molecules (7). Leucine, isoleucine, and valine are three branched chain amino acids (BCAAs) that are consistently linked to the incidence of type 2 diabetes mellitus (T2DM). Insulin resistance develops as a result of excessive food intake, increased gut microbial proliferation, and decreased BCAA catabolism (8). Based on these results, the study's hypothesis was to determine whether branched chain amino acids could predict glycemic intolerance in patients with impaired glycemic tolerance, those with type 2 diabetes mellitus who have had the disease for more than five years, and those who have just received a diagnosis.

Type 2 Diabetes mellitus is regarded as a chronic complex multifactorial disease which includes genetic, lifestyle and environmental factors (7). The epidemicity of this disease has affected both developed and developing countries alike. Prediabetes defined as blood glucose levels above normal but below the threshold of diabetes is increasing globally over the years (6). The global prevalence of impaired glucose tolerance in the year 2021 was 9.1% and is projected to increase to 10.0% in the year 2045 (9). The development of chronic complications of diabetes, either micro or macro vascular, can begin earlier in the pre-diabetes phase. Initially, a decrease in insulin production will cause a rise in postprandial glucose; but, over time, a further deterioration in β cell activity will also result in an increase in fasting glucose (10). The three essential amino acids—leucine, valine, and isoleucine—known as BCAAs primarily regulate protein and energy metabolism (11). Nonetheless, the association between BCAA and type 2 diabetes has been linked in numerous research. Dipeptidyl peptidase inhibitors, a hypoglycemic drug, significantly altered the amino acid pattern in mice fed a high-fat diet, according to a 2019 study by Xiaoyu Liao et al., particularly by lowering the quantity of the BCAA valine. Furthermore, patients with type 2 diabetes had much greater levels of valine in their blood (11). Deirdre's (2018) study was revealed that independent of risk factors, higher diet and plasma BCAA concentrations were associated with an increased incident T2D risk (7). Qingquan Ma *et al.*, 2020 also in his study found that the body weight, serum triglyceride level, white adipose tissue weight, and glucose and insulin intolerance were significantly elevated by valine supplementation in high-fat diet-fed mice (12).

AIM

To study the biochemical expression of Branched chain amino acids in predicting the glucose intolerance among individuals with various glycemic status**.**

OBJECTIVE

- To estimate the levels of Branched chain amino acid among impaired glycemic tolerance, newly diagnosed type 2 diabetes mellitus patients and Type 2 Diabetes mellitus patients with more than 5 years duration.
- To correlate the levels of Branched chain amino acid with anthropometric and biochemical parameters like Body mass index, blood glucose (fasting and post prandial) and glycated hemoglobin (HbA1c) among impaired glycemic tolerance, newly diagnosed type 2 diabetes mellitus patients and type 2 Diabetes mellitus patients with more than 5 years duration.

MATERIALS & METHODS

Type of Study: Prospective observational study
Sample size:
Group 1 (Prediabetics): 30
Group 2 (Newly diagnosed diabetics): 30
Group 3 (Type 2 Diabetes mellitus – more than 5 years duration): 30
Sampling Method: Convenient sampling
Study Duration: 4 months (November 2023 to February 2024) in a Tertiary Care Hospital at Puducherry

Inclusion criteria:
Group 1: Prediabetes

- Subjects with impaired fasting glucose (100-126mg/dl)
- Subjects with impaired glucose tolerance (≥140 and <200 mg/dl)
- Individuals will be provided with the Indian Diabetes risk score (IDRS) questionnaire. Those who have a score of >30 will be considered.

Group 2: Newly diagnosed type 2 Diabetes mellitus
Group 3: Type 2 Diabetes mellitus patients with

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more than 5 years duration

Exclusion criteria:

- Pregnant women
- Critically ill patient
- Individuals with IDRS score of less than 30

Ethical consideration: The study was commenced after getting prior consent from the Scientific Review Committee and from the Institutional Ethics Committee of the institution (EC/NEW/INST/2024/PY/0418).

Questionnaire: A self-assessment questionnaire was given to the patient to be filled that had the information's related to IDRS like age, family history of Diabetes and physical activity, measurement of height, weight, Body mass Index (BMI), and waist circumference.

Method of sample collection and processing: 5ml of venous blood was drawn under aseptic precautions in EDTA and plain tubes. Serum was separated by centrifugation and was analyzed for Blood glucose and Branched chain amino acid. EDTA blood was used to estimate HbA1c.

Blood Glucose: Fasting and Postprandial-GOD-POD Method (Colorimetric assay) was done using standard kits in the autoanalyser.

HbA1C: Immuno turbidity method.

Branched chain Amino acid: Colorimetric assay was done using standard kits in the autoanalyser.

STATISTICAL ANALYSIS

Continuous variables were reported as mean ±SD, and categorical variables as number and percentage. Data were compared amongst groups by one-way ANOVA (numerical variables). Associations between variables were assessed by Pearson's correlation. All statistical analysis were done using SPSS package 23.0

OBSERVATIONS & RESULTS

A cross-sectional study was conducted with 90 pre diabetic and type 2 Diabetic patients who were divided into 3 groups (Table 1, 2 &3; Figure 1)

- GROUP I: Impaired glycemic tolerance patients (30)
- GROUP II: Newly diagnosed Type 2 Diabetic patients (30)
- GROUP III: Type 2 Diabetic patients of more than 5 years duration (30)

Table 1: Baseline characteristics of the patients of various groups

	Group 1 (Prediabetes)	Group 2 (Newly diagnosed T2DM)	Group 3 (T2DM > 5 years)
Age	42 ±11.18	43 ± 8.72	55 ± 12.59
Sex	Male = 16 Female = 14	Male = 17 Female = 13	Male = 17 Female = 13
BMI	27.4 ± 4.62	29.45 ± 4.9	28.4 ± 5.31
Waist circumference	96 ± 19.01	106 ± 18.3	102 ± 16.87
Family History of DM	Yes = 20 No = 10	Yes = 21 No = 9	Yes = 14 No = 16
Physical activity	Yes = 5 No = 25	Yes = 1 No = 29	Yes = 6 No = 24

Table 2: Compare the mean values of HbA1c, Blood glucose (FBS, PPBS), BCAA, BMI and Waist circumference between the 3 groups

	Group 1 (Prediabetes)	Group 2 (Newly diagnosed T2DM)	Group 3 (T2DM > 5 years)	P value
Fasting blood glucose (mg/dl)	106 ± 10.07	171 ±34.53	159 ±31.63	0.000**
Post prandial glucose (mg/dl)	141 ±12.99	234 ± 49.09	245 ±42.62	0.000**
HbA1c %	6.1 ±0.36	8.84 ±1.29	9.1 ±1.32	0.000**
BCAA (µ mol/L)	996.5 ±101.19	825.5 ±253.30	539.4 ±94.30	0.000**
BMI	27.4 ± 4.62	29.45 ± 4.9	28.4 ± 5.31	0.312
Waist circumference	96 ± 19.01	106 ± 18.3	102 ± 16.87	0.116

**** - highly significant (p value - <0.001)**

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Table 3: Correlation between BCAA and HbA1c, FBS, PPBS, BMI, WC

	BCAA	
HbA1c	Pearson's correlation	-.514**
	Sig 2 tailed	0.000
	N	90
FBS	Pearson's correlation	-.396**
	Sig 2 tailed	0.000
	N	90
PPBS	Pearson's correlation	-.527**
	Sig 2 tailed	0.000
	N	90
BMI	Pearson's correlation	.082
	Sig 2 tailed	.445
	N	90
WC	Pearson's correlation	.001
	Sig 2 tailed	.994
	N	90

**** - Correlation is significant at the 0.01 level (2 tailed)**

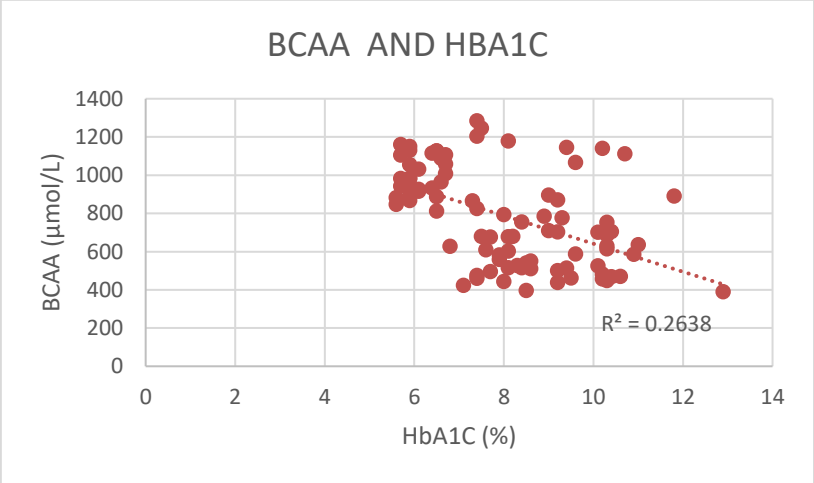

Figure 1: Scatter diagram showing correlation between HbA1c and BCAA

DISCUSSION

A highly common metabolic disease, type 2 diabetes mellitus is characterized by abnormalities in the metabolism of carbohydrates, fats, and amino acids that arise from both insufficient insulin secretion and resistance to the action of insulin (13). Pre-diabetes, sometimes referred to as early diabetes, appears to rise proportionately and has a high risk of turning into type 2 diabetes (6). In both humans and animals, BCAAs—essential amino acids—play important metabolic and regulatory roles. They promote intestinal health, mammary health, metabolic regulation, and protein synthesis (14). Nonetheless, numerous investigations have demonstrated that BCAA are linked to the development of type 2 diabetes mellitus (T2DM) and may play a role in the pathophysiology of insulin resistance (8). Therefore, the goal of the current investigation was to identify the biochemical expressions of Branched chain amino acid among impaired glycemic tolerance (pre-diabetes), newly diagnosed type 2 diabetes mellitus patients and type 2 Diabetes mellitus patients with more than 5 years duration. The patients were divided into 3 groups of 30 each respectively. On comparing the mean values of HbA1c, Blood glucose (FBS & PPBS), BCAA, BMI and Waist circumference, there was a significant correlation among the 3 groups for blood glucose, HbA1c and BCAA. Also there exist a strong negative correlation of the BCAA concentration with HbA1c (r value: -0.5.14), FBS(r value: -0.396), PPBS (r value: -0.527), between prediabetes and chronic diabetes patients. The levels of BCAA is very much high among pre-diabetics when compared to T2DM patients. The potential basis behind this increased level of BCAA concentration includes high dietary consumption, increased production by gut microbes as well as diminished BCAA catabolism in muscle and adipose tissues (15). Wang TJ, *et al.*, (2011) found in his study that the fasting concentration of amino acids were elevated up to 12 years prior to the onset

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of diabetes and the risk of diabetes increased 4 fold with elevated concentration of amino acids in blood (16). According to the study conducted by Jagdish Vangipurapu *et al.*, (2019) BCAA were found to be significantly associated with an increased risk of incident type 2 diabetes after adjustment for confounding factors. In his follow up study, he found that isoleucine, and valine were associated with reduced insulin secretion and increased fasting and 2-h glucose levels an important contributor in the conversion to diabetes (17). This result is similar to our study. Because compared to chronic T2DM patients receiving treatment for the same condition, prediabetes patients with reduced insulin production and insulin resistance had higher levels of BCAA. When BCAA catabolism is impaired, potentially harmful intermediates build up, which leads to beta cell malfunction and ultimately beta cell death. This implies that AAs may negatively impact insulin secretion, which in turn may affect the risk of type 2 diabetes and hyperglycemia (18). In a similar vein, Waldford et al. (2013) found that when taking Glipizide and Metformin for type 2 diabetes, the concentration of BCAA levels altered dramatically (19). The results mentioned above are concurrent with our findings. Hence screening for the concentration of BCAA levels among prediabetes people can be strongly suggested to predict the development of incident type 2 diabetes mellitus.

CONCLUSION

The transition from early metabolic abnormalities that happens in prediabetes to diabetes takes many years yet majority of the individuals eventually develop diabetes. The risk of developing long term complications of diabetes is also related to its duration and the level of glycemia. Hence, screening for prediabetes becomes mandatory. The rapid rise in prediabetes worldwide raises urgent needs to develop effective prognostic biomarkers. There exists a correlation between metabolites especially Branched chain amino acid with blood glucose and insulin resistance. The risk of diabetes will increase several folds in those patients with high BCAA level. Hence BCAA can be considered as an important metabolite marker in assessing the glycemic tolerance among prediabetes patients.

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