Review Article

A STUDY OF THE ASSOCIATION BETWEEN BRAIN DERIVED NEUROTROPHIC FACTOR AND METABOLIC SYNDROME: A PRELIMINARY SYSTEMATIC REVIEW AND META-ANALYSIS OF CASE-CONTROL STUDIES

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ABSTRACT

Background*: Metabolic Syndrome (MetS) is defined by a combination of cardiovascular risk factors including elevated central obesity, triglycerides, fasting blood glucose, blood pressure and reduced levels of high density lipoproteins leading to an increased risk of heart disease, stroke, diabetes and associated mortality. Brain Derived Neurotrophic Factor (BDNF) has been hypothesized and studied in the pathophysiology of MetS. Our objective was to quantitatively compare the concentrations of BDNF in MetS diagnosed patients and healthy controls.*

Methods: *A systematic review and Meta analysis was conducted using selected case control studies from a database search of scientific literature up to August 2015 and a search of the references.*

Results: *A total of 5 case control studies that measured BDNF concentrations in MetS patients diagnosed by the ATP III criteria for metabolic syndrome were analyzed. Significantly reduced levels of BDNF was observed, ($p<0.05$) weighted mean difference of 0.809ng/ml (99% CI: 0.067 to 1.551), in MetS patients compared with the control subjects (231 non MetS and 312 MetS subjects).*

Conclusions: *This meta analysis reports reduced levels of BDNF in Metabolic syndrome. With past studies reporting a majority of positive results, the results of this study help strengthen evidence of the significance of BDNF in the pathophysiology of MetS.*

Keywords: *Brain derived neurotropic factor, metabolic Syndrome, meta analysis. pathophysiology.*

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INTRODUCTION

Metabolic syndrome, with a worldwide prevalence ranging from less than 10% up to 84%[1] is considered a risk factor for cardiovascular disease, diabetes mellitus[2] and some kinds of cancer.[3] ATP III stipulates that the presence of at least three of the five criteria: waist circumference of >102 cm (men); >88 cm (women), triglycerides level >150 mg/dL, HDL cholesterol <40mg/dl (men); <50mg/dl (women), blood pressure of >130/>85 mmHg or a fasting glucose of >110 mg/dL, indicates metabolic syndrome.

Clinical management of MetS includes the first line therapy of lifestyle modifications focusing on modification of the underlying risk factors of overweight and obesity, physical inactivity, and an atherogenic diet. Second line drug therapy is required to achieve the recommended goals set after a risk assessment. The American Heart Association conference on scientific issues related to definition highlighted the need for a better understanding of the genetic and metabolic contributors to the development of the syndrome underscoring the need for studies on the factors hypothesized in the pathology of MetS.[4]

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Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, which includes Nerve Growth Factor (NGF), neurotrophin-3, and neurotrophin-4/5. The neurotrophic and metabotrophic effects of BDNF and NGF are well known; their role in metabolic syndrome is however, not as well established. The metabotrophic effects are involved in the maintenance of glucose and lipid metabolism, dysregulation of which leads to the development of MetS.

These reduced levels can thus be implicated in the pathogenesis of MetS as explained by the consequential metabotrophic deficit.[5] Various hypotheses have also been put forth in this regard.[6-8] Studies have reported reduced BDNF and NGF levels in MetS, DM and obesity.[9-15] Studies also report that the effective prevention and treatment of metabolic syndrome could be important for the prevention of depression.[16] Aside from evidencing that these disorders could all be linked; this finding also pans out the need for markers for the diagnosis of MetS which could be a risk factor for the other disorders.

The primary aim of this meta-analysis was to determine the role of BDNF in Metabolic Syndrome by assessing its levels in population groups with and without Metabolic Syndrome.

In spite of multiple studies reporting reduced levels of BDNF in association with MetS, a generalizable pattern of BDNF level alteration is yet to be established. Therefore, this study aims to improve the strength of the evidence obtained from individual studies by determining

the changes in the concentrations of BDNF in the MetS diagnosed subjects and non MetS controls using meta analysis techniques.

METHODOLOGY

A literature search of scientific literature in English was done using PUB MED, Science direct, Clinical key, Cochrane and Google scholar with a cross reference search also done. Articles up to August 2015 were searched using the key words BDNF, Metabolic Syndrome, Neurotrophins and Metabolic parameters. Only original articles that recorded measurements of BDNF in MetS and non MetS subjects were selected. Articles were included if the subjects met the ATP III criteria for metabolic syndrome. Articles needed to be published in English language, with the subjects reporting no co morbid conditions and had to be studies carried out in adult patients. Studies done in diabetic populations were excluded, those that included physical interventions were also excluded as this may reflect the changes in BDNF levels due to physical exertion, a fact that is well established.

Eligibility assessment of these articles was performed independently in an unblended standardised manner by four reviewers. Disagreement between the reviewers was resolved by the fifth reviewer.

STUDIES INCLUDED

A total of 5 case control studies, (I-Te Lee et al., Monica Bullo et al.,G.N Chaldakov.,et al., Mariyana G Hristova and Kanjana,et al.)[17-21] including 543 subjects were finally included. Among these studies, 2 were conducted in the Asian population and 3 were conducted in the European population. All included studies reported significantly lower concentrations of BDNF in the MetS group in comparison with healthy volunteers with the exception of I-Te Lee et al., that reported an insignificant P value.

I-Te Leeet al., included thirty-four non-diabetic men with MetS and another 24 age-matched men without MetS. They reported no significant difference in serum BDNF concentrations between men with or without MetS (40.9±8.0 vs. 43.2±6.1 ng/ml, P=0.235).

Mariyana G Hristova compared 40 patients with MetS to 10 age-matched controls.

BDNF levels were significantly lower in MetS patients than in controls (2.790±0.880 vs. 2.721±0.878 ng/ml, P<0.05).

Monica Bullo et al., assessed 55 female patients with MetS and 25 healthy females. BDNF levels were found to be significantly lower in MetS patients compared to the healthy volunteers (4.000±2.600 vs. 2.400±3.400, P<0.05).

G.N Chaldakov.,et al., reported significantly lower BDNF levels in the 23 MetS patients in comparision to the 10 age matched healthy controls (8.698±0.391 vs. 7.013±0.389 ng/ml, P<0.05).

Kanjana,et al compared 160 MetS patients and healthy volunteers and reported a significantly lower level of BDNF in the MetS group. (13.850±7.720 vs. 13.350±7.330 ng/ml, P<0.05).

Two independent reviewers extracted the data for mean and standard deviation BDNF measurements for each group of metabolic syndrome and control. For the study in which data was provided in median and range, mean and standard deviation was calculated.

The 'Comprehensive Meta-Analysis-3.0' software was used for performing the meta analysis. Standard differences in mean with 99% CI for continuous variables were used to assess the concentrations of BDNF in MetS. For continuous outcomes data, a weighted mean difference and 99% confidence intervals was calculated using random effects model. This model gives a wider confidence interval compared to the fixed effects model, when a significant heterogeneity among the studies is expected.

Heterogeneity and publication bias:

Heterogeneity between the studies was tested by using Random effect model. The 'between study' heterogeneity was tested using I^2 statistics and a p-value less than 0.05 was considered significant. Likely sources of heterogeneity such as age, gender, duration of illness and ethnicity were investigated.

RESULTS

A total of 936 articles were identified for review. 26 articles were initially selected based upon inclusion and exclusion criteria. Of these 21 articles were excluded. These were the studies whose participants reported co morbid conditions, studies performed on animals and studies in polymorphisms. One article was hand searched from the Journal of diabetology and Metabolic Syndrome. Studies were excluded based upon the presence of co-morbid conditions[17] studies that includedphysical interventions[18-20]genetic polymorphism studies[21-25] and studies that reported data in a graphical format.[12] A total of 5 case control studies(Table-1), (I-Te Leeet al.,Monica Bullo et al.,G.N Chaldakov.,et al., Mariyana G Hristova and Kanjana,et al.)[11,13,14,15,26] including 543 subjects were finally included in the systematic review and meta analysis. BDNF concentrations were reported in ng/ml.

BDNF and Metabolic Syndrome

BDNF measurements were extracted from 5 studies including 231 non MetS and 312 MetS subjects (Table.2). From the forest plot (Fig.1), significantly lower concentrations of BDNF in subjects with Metabolic Syndrome in comparison with non Metabolic Syndrome subjects, with an overall standard difference in means of 0.809ng/ml (95% CI:0.067 to 1.551; p=0.033) was observed.The effect size was found to be uniform in all the studies, except in the study conducted by Monica Bullo et al., and G.N Chaldakov.,et al., which reported higher

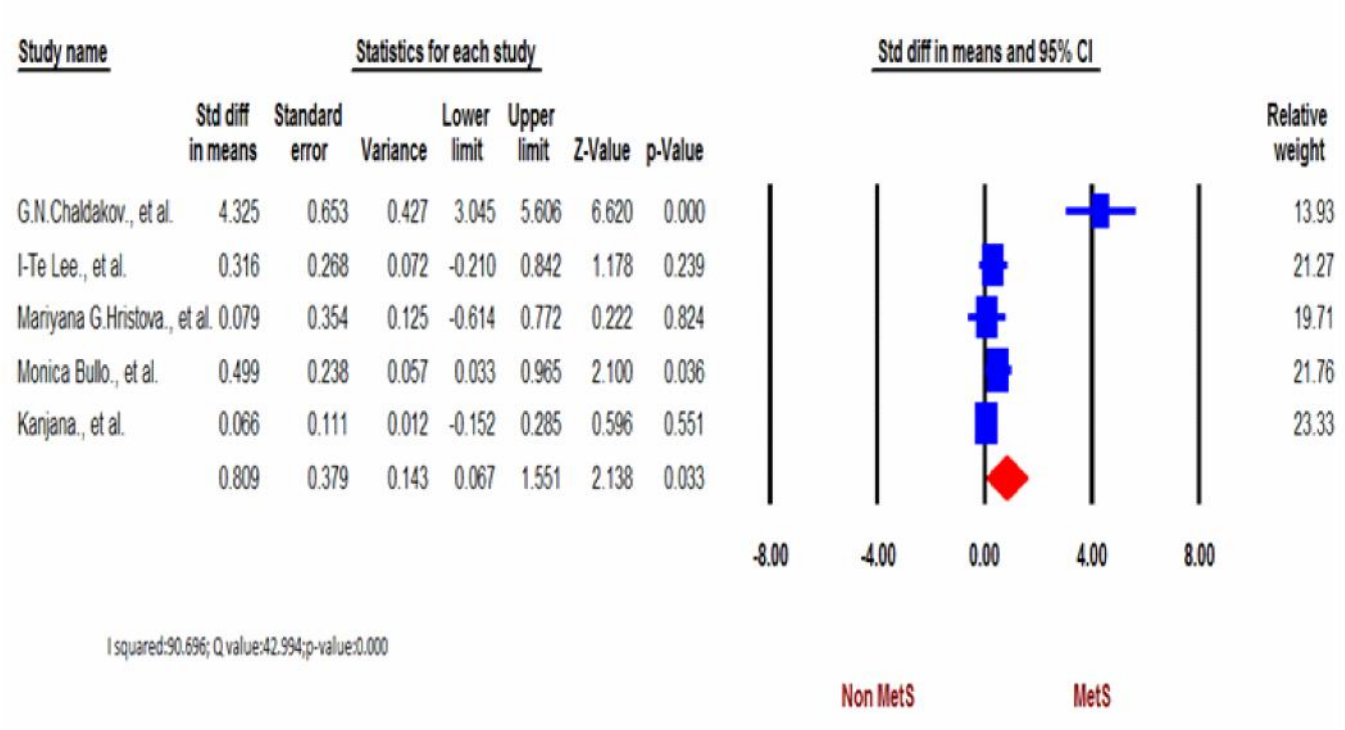

Fig. 1: Forest plot of the association between BDNF level in Non MetS and MetS patients.

Table 1: Basic characteristics of trials included in systematic review and meta-analysis

AUTHOR	YEAR	NO. OF PATIENTS	SAMPLE	GENDER	AGE	PARAMETERS MEASURED
G.N Chaldakov *et al.*	2001	33	Mets-23 Non Mets- 10	Mets 3M, 20F Non Mets 3M, 7F	55-60	BDNF NGF LEPTIN
I-Te Lee *et al.*	2012	58	Mets -34 Non Mets- 24	Mets 34M, 0F Non Mets 24M, 0F	20-75	BDNF LEPTIN CRP
Mariyana G. Hristova.	2011	95	Mets- 40 Non Mets -10	Mets 0M, 40F Non Mets 0M, 10F	43-45	BDNF NGF CRP
Monica Bullo *et al.*	2007	80	Mets-55 Non Mets-25	Mets 0M, 55F Non Mets 0M, 25 F	18-65	BDNF NGF
Kanjana *et al.*	2014	322	Mets -163 Non Mets -162	Mets 73M, 87F Non Mets 86M, 76F	24-64	BDNF LEPTIN

effect sizes and consequently more significant p values. All studies had comparable relative weight except G.N Chaldakov.,et al., which had a slightly lower value.

Heterogeneity and publication bias

The Eggers test was performed (p=0.07212) which indicated a statistically significant asymmetry.[27] The heterogeneity test gave an I^2 value of 90.696% which indicates considerable heterogeneity, p value of <0.05 (0.000) and Q value of 42.994.

DISCUSSION

Metabolic Syndrome, in the clinical setting, is diagnosed as the manifestation of a cluster of cardiovascular components. Nowadays modern medicine is using IR, CRP, and HbA1C level as markers for MetS. However there is still a lack of a reliable biomarker for the conclusive diagnosis of MetS. We hence studied the significance of BDNF in relation to MetS. This may provide a marker for future clinical use.

Table 2: Data extracted from articles with regard to BDNF Non MetS and MetS patients.

STUDY NAME	Non Mets	Column1	Mets	Column2
	N	Mean±S.D (ng/ml)	N	Mean±S.D (ng/ml)
G.N.Chaldakov *et al.*	M=3 F=7	8.698±0.391	M=3 F=20	7.013±0.389
I-Te Lee *et al.*	M=24 F=0	43.200±6.100	M=34 F=0	40.900±8.000
Mariyana G. Hristova.	M=0 F=10	2.790±0.880	M=0 F=40	2.721±0.878
Monica Bullo *et al.*	M=0 F=25	4.000±2.600	M=0 F=55	2.400±3.400
Kanjana *et al.*	M=86 F=76	13.850±7.720	M=73 F=87	13.350±7.330

Our study indicates that the levels of Brain Derived Neurotrophic Factor are decreased in Metabolic Syndrome. The mechanism behind this may be explained by the numerous previously made observations. BDNF has been proven to have a role in the functions of energy balance.[15] Together with leptin, it has been indicated in energy homeostasis.[28,29] This is presumably due to its significance in obesity and insulin resistance,[10,28] both of which are components of MetS. Although it is well established that BDNF has specific effects on signalling pathways involved in appetite regulation,[29,30] it has been found from animal studies that BDNF has effects on metabolism that are not mediated solely via appetite regulation.[31] It has also been observed from animal experiments, that, by suppressing PPAR-alpha and fibroblast growth factor 21, BDNF might facilitate insulin resistance and dyslipidemia and thus has anti-diabetic and lipid lowering effects.[32] Supporting this is the finding that the cerebral output of BDNF is negatively regulated by high plasma glucose levels.[28]

Another mechanism is that BDNF may operate as metabotrophins, involved in the maintenance of cardiometabolic homeostasis (glucose and lipid metabolism as well as energy balance, cardioprotection, and wound healing).[5]

Substantial heterogeneity observed within studies could be attributed mainly to the diverse ethnicities of the study population and the variability of procedures used for BDNF measurement.

An interesting finding in our study is the radically altered levels of BDNF in relation to gender in the control population used. The BDNF levels were significantly elevated in men when compared to women.[11,12,14] This is supported by previous findings that gender may affect the levels of BDNF.[33,34,35] The exact mechanism of this is however still unknown.

The present study is limited by the small subject population used due to the scarce number of studies conducted in the topic and also by significant statistical heterogeneity.

The significantly altered level of BDNF with gender is another observation that demands scrutiny. Altogether, the fact that BDNF reduction may be implicated in Metabolic Syndrome has been established and further studies to assess the role of the other neurotrophins hypothesized to be linked to MetS is entailed.

In conclusion, our study indicates that metabolic syndrome can be associated with a decreased level of circulating BDNF. Our results indicate that this can be used to identify the disorder thus illustrating the clinical significance of BDNF as a marker. However, whether this is a part of the aetiology or a consequence of developing metabolic syndrome, remains to be investigated.

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