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Alterations of Brain-Derived Neurotrophic Factor and Creatinine During Ramadan Fasting: A Prospective, Controlled Clinical Trial

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Abstract

Background: Brain-derived neurotrophic factor (BDNF) is associated with mood-related symptoms. Fasting can improve mood. However, there was a lack of information about BDNF during prolonged fasting in Summertime in Germany.
Objectives: This study aimed to determine (1) the effect of Ramadan fasting on BDNF and creatinine during the month of Ramadan in Germany; (2) the correlation of BDNF with body composition parameters and Health-related Quality of Life (HQoL).
Methods: This prospective controlled clinical trial was conducted on a total of fifty healthy adult male during Ramadan 2015 in the Department of Rehabilitation Medicine affiliated to Hannover Medical School, Hannover, Germany. The participants were recruited and divided into two groups, including fasting (FG) and non-fasting groups (NFG). The FG was evaluated at T1: one week before Ramadan, T2: mid of Ramadan, T3: last days of Ramadan, and T4: one week after Ramadan. The NFG was evaluated only at T1 and T3.
Results: No significant differences were found between FG and NFG at T1 or T3 with regard to BDNF and creatinine ($P > 0.05$). In the FG, significant alterations were demonstrated in terms of BDNF. The BDNF was significantly increased at T3 compared with T2 ($P < 0.05$). No significant change of creatinine was seen in the FG ($P > 0.05$).
Conclusions: It seems BDNF plays a role in the Ramadan fasting. Normal range level of creatinine suggested that long-period Ramadan fasting is safe for the kidney of healthy male subjects.

Keywords: Body Composition, Brain-Derived Neurotrophic Factor, Creatinine, Fasting, Kidney, Mood, Ramadan, Quality of Life

1. Background

Ramadan fasting (RF) has been known to be of great physical and psychological benefits to healthy people (1-5). Islamic fasting period follows the lunar calendar, which varies according to geographical location. In Germany, the fasting period during Ramadan 2015 was about 18 to 19 hours per day.

Fasting has also an effect on mood-related symptoms (6-8). Mood-related symptoms are associated with the brain-derived neurotrophic factor (BDNF) (1, 9, 10). Moreover, BDNF plays a role in different types of neuronal functions and is shown to be influenced by nutritional intake, fasting, and exercise (11).

However, there is a lack of information about the impact of RF on BDNF and how it correlates with mood. During RF, liquid intake is also forbidden, which can cause serious damage to the kidneys resulting in renal dysfunction.

2. Objectives

Therefore, this study aimed to (1) determine the effects of RF on serum levels of BDNF and creatinine; (2) the correlation of BDNF with mood and health-related quality of life (HQoL). We hypothesized that BDNF would be altered during RF.

3. Methods

This study was a prospective controlled trial. The study was approved by the Ethics Committee of Hannover Medical School, Germany (Ethics No. 6899). This study was performed in accordance with the Ethical Standards laid down in the 1964 Declaration of Helsinki. All patients agreed to participate after informed consent. This study was conducted on Ramadan 2015, June-July 2015. The study center was the Department of Rehabilitation Medicine, Hannover Medical School, Hannover, Germany, and this study

has been registered in the German Registry of Clinical Trial with DRKS-ID: DRKS00008181.

3.1. Participants

3.1.1. Inclusion and Exclusion Criteria

Inclusion criteria for fasting group (FG) were (1) healthy (particularly not suffering from any form of chronic disease, pain or psychiatric diagnosis); (2) male; (3) older than 18 years of age, (4) intent on fasting the whole month of Ramadan (5) proficient in German/English. The non-fasting group (NFG) had the same inclusion criteria with the exception that the participants were not fasting.

3.1.2. Assessment Time Points

To assess our endpoints, four time-points were assigned:

T1: one week before the start of Ramadan (June 2015); T2: mid of Ramadan; T3: last days of Ramadan, and T4: one week after Ramadan. In the FG, all participants were assessed at all 4 time points, while the NFG were only assessed at T1 and T3.

3.1.3. Evaluation Parameters

Peripheral venous blood samples were collected from both FG and NFG in serum tubes (Monovette, Sarstedt, Germany) between 08:00 and 10:00 hours. Samples were allowed to clot before being centrifuged at 1500 g for 15 min. Serum samples were stored at -80°C until analyses.

3.2. BDNF

Serum samples were measured using commercial enzyme immunoassay according to the manufacturer's instruction kit (Cusabio-CSB-E04501H, Hölzel Diagnostika Handels GmbH, Köln, Germany).

3.3. Creatinine

Serum creatinine levels were analyzed according to the manufacturer's protocol (Cobas Substrates, Creatinine plus ver.2, Roche Diagnostics GmbH, Mannheim, Germany).

3.4. Questionnaires Related to Mood and HQoL

SF-12 for (HQoL), Beck's Depression Inventory (BDI)-II, and Hospital and Anxiety Depression Scale (HADS-D) were used for depression score measurement; the fatigue was measured using Visual Analogue Scale (VAS) and Fatigue Severity Scale (FSS); sleep problem was also measured by the Epworth Sleepiness Scale (ESS). We had previously reported on the effect of fasting on HQoL (1). In this article, the correlations between HQoL and BDNF were explored.

3.5. Statistical Analysis

Statistical analysis was performed by using IBM SPSS Software for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). The Shapiro-Wilk test was used to check the normality of the data. Friedman test was used to compare significant differences between different time points (followed by post-hoc test with Bonferroni correction). Student's *t*-test or Mann-Whitney U test was used to compare baseline levels of FG and NFG at the T1 and T3 time points. The mean imputation method was used for handling missing values. Explorative statistical analyses such as the correlation of biological mediators and body composition parameters, mood, fatigue, sleepiness and health-related QoL of the subjects were performed. Statistical significance was set at $P < 0.05$.

4. Results

There are no significant differences between FG and NFG at baseline with regard to age, height, body weight, BDNF, and creatinine (Table 1).

There is no significant difference between the FG and NFG in terms of both BDNF and creatinine levels (Figure 1A and B). Interestingly, the level of BDNF was significantly increased in the FG at T3 as compared to T2 ($P < 0.05$) and returned to the baseline value at T4. Although the level of creatinine was increased at T2, there was no significant difference between time points in the FG. Significant correlations of BDNF and mood could not be observed at all time-points ($P > 0.05$).

5. Discussion

The purpose of this study was to determine the alterations of BDNF and creatinine during RF. Our results demonstrate that there are no significant differences between the FG and NFG in both BDNF and creatinine. Interestingly, significant alterations of BDNF occurred in FG during RF.

In this study, BDNF level was decreased at T2 and increased at T3 and returned to the same level as the baseline (T1) at T4. It seems that on T2 and T3, BDNF showed an adaptation process, which led to the alteration of BDNF level. The BDNF has been known to be associated with mood-related disorders (12, 13). The RF could alleviate mood in both healthy subjects and patients (1, 14). However, we could not observe significant correlations between BDNF, mood, and HQoL. This difference can potentially be explained by the inclusion of clinically depressed patients in previous studies, while only healthy subjects were recruited to our study.

Table 1. Characteristics of the FG and NFG at Baseline[a, b]

	Group		P Value
	FG	NFG	
Age and race			
Age, y	26.12 ± 0.98	26.20 ± 0.98	0.977
White/Asian	21/4	16/9	0.196[c]
Body composition			
Height, cm	177.20 ± 1.41	178.16 ± 2.12	0.884
Body weight, kg	77.82 ± 2.46	76.16 ± 4.29	0.739
BMI, kg/m^2	24.78 ± 0.73	24.56 ± 0.78	0.84
Mood and HQoL			
Anxiety (HADSA)	4.92 ± 3.82	4.26 ± 3.38	0.521
Depression (HADS D)	4.36 ± 3.88	3.06 ± 3.47	0.218
Depression (BDI-II)	8.36 ± 8.21	6.48 ± 5.97	0.359
Physical health (SF-12)	52.60 ± 5.35	53.67 ± 3.64	0.414
Mental health (SF-12)	49.48 ± 10.83	49.23 ± 11.12	0.936
Fatigue and sleepiness			
Fatigue (VAS)	3.01 ± 1.83	3.08 ± 1.96	0.893
Fatigue severity scale (FSS)	26.92 ± 8.65	26.44 ± 10.38	0.86
Epworth sleepiness scale (ESS)	7.96 ± 3.81	7.16 ± 3.73	0.457
BDNF, ng/mL	47.00 (20.00 - 70.50)	51.00 (14.00 - 62.00)	0.877
Creatinine, μmol/L	84.00 (71.10 - 92.30)	88.03 (81.25 - 98.95)	0.509

Abbreviations: IQR, iInterquartile range; SEM, standard error of mean; VAS, visual analogue scale.
[a] Values are expressed as mean ± SEM or median (IQR).
[b] Age, height and body weight were analysed using the Student's *t*-test. The BDNF and creatinine were analysed using the Mann-Whitney U-test.
[c] Fischer's exact test.

Previous studies reported on the association of BDNF with body weight and fat both in animal and human subjects (1, 15). Body weight and fat percentage altered in RF (1); however, this alteration did not correlate with circulating BDNF levels. The reported correlations (15) recruited obese participants, whereas the participants were mostly healthy and non-obese in the current study.

Creatinine is a marker related to glomerular filtration rate function (16). Fasting for long periods of time, particularly during summer months, has previously been postulated to lead to kidney impairment as a result of drastically reduced fluid intake. Our results demonstrate that there is no significant difference in creatinine level between the FG and NFG. In the FG, serum creatinine levels tended to increase at T2, but returned to baseline levels at T3 and T4. It seems the increase at T2 was due to the physiological adaptation of fasting. Therefore, we hypothesize that RF during the summer months is tolerable to the kidney in healthy male subjects, but recommend that patients with specific health conditions (e.g., kidney disease), should undergo monitoring by health professionals (17, 18).

This study has several strengths and limitations. Best to our knowledge, this is the first prospective control study that reports BDNF and creatinine during long-period fasting. Recruiting only male participants increase the homogeneity of the study population. It has also several limitations, as the results could differ in different gender and age populations. Eating habits were not controlled, but this could be also a strength, as it could reflect the real condition of the participants. However, recording eating habits and caloric consumptions should be considered in the future. Two evaluation time points in the NFG were selected as our hypothesis that NFG would not have any changes during T2 and T4. Comparing before fasting (T1) and the last day of the fasting period (T3) was our main focus.

5.1. Conclusions

This study demonstrated no significant differences in terms of BDNF and creatinine between the FG and NFG. The BDNF was altered during RF in the FG. No significant

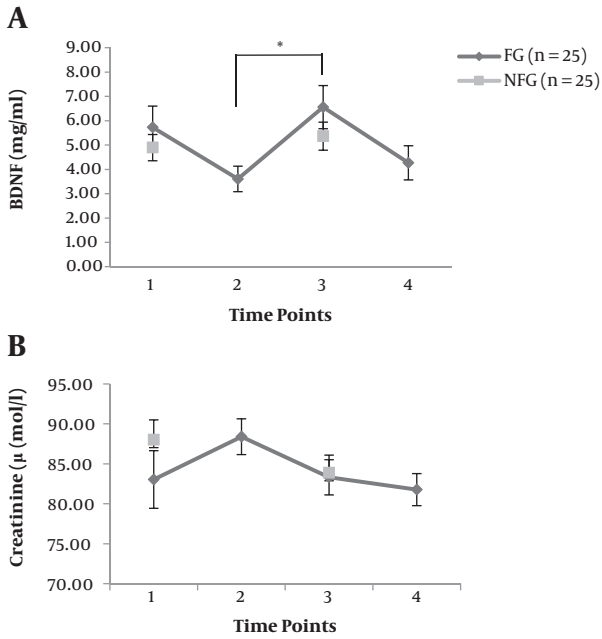

Figure 1. Effect of Ramadan fasting on serum BDNF (A) and serum creatinine (B) (*P < 0.05).

change in creatinine level establishes the tolerable situation for kidney in male healthy subject during a long-period of fasting.

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Footnotes

Clinical Trial Registration: This study has been registered in the German Registry of Clinical Trial with DRKS-ID: DRKS00008181.

Conflict of Interests: None.

Ethical Approval Code: The study was approved by the Ethics Committee of Hannover Medical School, Germany (Ethics No. 6899).

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References

1. Nugraha B, Ghashang SK, Hamdan I, Gutenbrunner C. Effect of Ramadan fasting on fatigue, mood, sleepiness, and health-related quality of life of healthy young men in summer time in Germany: A prospective controlled study. *Appetite*. 2017;**111**:38–45. doi: 10.1016/j.appet.2016.12.030. [PubMed: 28027907].
2. Samad F, Qazi F, Pervaiz MB, Kella DK, Mansoor M, Osmani BZ, et al. Effects of Ramadan fasting on blood pressure in normotensive males. *J Ayub Med Coll Abbottabad*. 2015;**27**(2):338–42. [PubMed: 26411111].
3. Norouzy A, Salehi M, Philippou E, Arabi H, Shiva F, Mehrnoosh S, et al. Effect of fasting in Ramadan on body composition and nutritional intake: A prospective study. *J Hum Nutr Diet*. 2013;**26 Suppl 1**:97–104. doi: 10.1111/jhn.12042. [PubMed: 23679071].
4. Lamine F, Bouguerra R, Jabrane J, Marrakchi Z, Ben Rayana MC, Ben Slama C, et al. Food intake and high density lipoprotein cholesterol levels changes during ramadan fasting in healthy young subjects. *Tunis Med*. 2006;**84**(10):647–50. [PubMed: 17193859].
5. Bogdan A, Bouchareb B, Touitou Y. Ramadan fasting alters endocrine and neuroendocrine circadian patterns. Meal-time as a synchronizer in humans? *Life Sci*. 2001;**68**(14):1607–15. [PubMed: 11263673].
6. Hussin NM, Shahar S, Teng NI, Ngah WZ, Das SK. Efficacy of fasting and calorie restriction (FCR) on mood and depression among ageing men. *J Nutr Health Aging*. 2013;**17**(8):674–80. doi: 10.1007/s12603-013-0344-9. [PubMed: 24097021].
7. Chtourou H, Hammouda O, Souissi H, Chamari K, Chaouachi A, Souissi N. The effect of ramadan fasting on physical performances, mood state and perceived exertion in young footballers. *Asian J Sports Med*. 2011;**2**(3):177–85. [PubMed: 22375237]. [PubMed Central: PMC3289213].
8. Michalsen A. Prolonged fasting as a method of mood enhancement in chronic pain syndromes: A review of clinical evidence and mechanisms. *Curr Pain Headache Rep*. 2010;**14**(2):80–7. doi: 10.1007/s11916-010-0104-z. [PubMed: 20425196].
9. Mondelli V, Cattaneo A, Murri MB, Di Forti M, Handley R, Hepgul N, et al. Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: A pathway to smaller hippocampal volume. *J Clin Psychiatry*. 2011;**72**(12):1677–84. doi: 10.4088/JCP.10m06745. [PubMed: 21672499]. [PubMed Central: PMC4082665].
10. Nugraha. Depressive symptoms, exercise, and brain-derived neurotrophic factor in fibromyalgia syndrome: A mini review. *J Autoimmune Dis Rheumatol*. 2013;**1**(1):19–23. doi: 10.12970/2310-9874.2013.01.01.4.
11. Walsh JJ, Edgett BA, Tschakovsky ME, Gurd BJ. Fasting and exercise differentially regulate BDNF mRNA expression in human skeletal muscle. *Appl Physiol Nutr Metab*. 2015;**40**(1):96–8. doi: 10.1139/apnm-2014-0290. [PubMed: 25494871].
12. Nugraha B, Korallus C, Gutenbrunner C. Serum level of brain-derived neurotrophic factor in fibromyalgia syndrome correlates with depression but not anxiety. *Neurochem Int*. 2013;**62**(3):281–6. doi: 10.1016/j.neuint.2013.01.001. [PubMed: 23318672].
13. Autry AE, Monteggia LM. Brain-derived neurotrophic factor and neuropsychiatric disorders. *Pharmacol Rev*. 2012;**64**(2):238–58. doi: 10.1124/pr.111.005108. [PubMed: 22407616]. [PubMed Central: PMC3310485].
14. Fond G, Macgregor A, Leboyer M, Michalsen A. Fasting in mood disorders: Neurobiology and effectiveness. A review of the literature. *Psychiatry Res*. 2013;**209**(3):253–8. doi: 10.1016/j.psychres.2012.12.018. [PubMed: 23332541].
15. Lee IT, Wang JS, Fu CP, Lin SY, Sheu WH. Relationship between body weight and the increment in serum brain-derived neurotrophic factor after oral glucose challenge in men with obesity and metabolic syndrome: A prospective study. *Medicine (Baltimore)*. 2016;**95**(43). e5260. doi: 10.1097/MD.0000000000005260. [PubMed: 27787389]. [PubMed Central: PMC5089118].

16. Harmoinen A, Lehtimaki T, Korpela M, Turjanmaa V, Saha H. Diagnostic accuracies of plasma creatinine, cystatin C, and glomerular filtration rate calculated by the Cockcroft-Gault and Levey (MDRD) formulas. *Clin Chem*. 2003;**49**(7):1223–5. [PubMed: 12816933].
17. El-Wakil HS, Desoky I, Lotfy N, Adam AG. Fasting the month of Ramadan by Muslims: Could it be injurious to their kidneys? *Saudi J Kidney Dis Transpl*. 2007;**18**(3):349–54. [PubMed: 17679744].
18. Bragazzi NL. Ramadan fasting and chronic kidney disease: Does estimated glomerular filtration rate change after and before Ramadan? Insights from a mini meta-analysis. *Int J Nephrol Renovasc Dis*. 2015;**8**:53–7. doi: 10.2147/IJNRD.S61718. [PubMed: 26082658]. [PubMed Central: PMC4459622].