Jundishapur Journal of Physiology (JJP). **2018 Oct; 1(2); 76-80**

Published online 2018 Oct 20. **Original Paper**

Effect of Vitamin B3 on Iron and Plasma cortisol in Postpartum Depression in Female Mice

Marzieh Abin[1], Maryam Rafiei Rad[*1], Saeed Valipour Chahardachrik[1]

1. Department of Biology, Faculty of Basic Sciences, Izeh Branch, Islamic Azad University, Izeh, Iran.

*Corresponding Author: Maryam Rafiei Rad, Department of Biology, Faculty of Basic Sciences, Izeh Branch, Islamic Azad University, Izeh, Iran.

Cell phone: +989163116542, Fax: +9843643374
Email: Rafieirad.m@gmail.com

Received: May 28, 2018; Revised: Aug 12, 2018; Accepted: Sep 27, 2018

Introduction: change in cortisol levels and low iron levels after childbirths one of the major factors that exacerbate postpartum depression in women. The B-vitamins as a supplement can be effective in treating this disorder. The aim of this study was to investigate the effect of The B3 vitamin on plasma cortisol and blood iron levels in postpartum depression in adult female mice.

Materials and Methods: In this study, 50 female mice of NMRI strain were divided into 5 groups (n = 10) including the control group, postpartum depression group, and groups of postpartum depression and treatment with doses of 50, 100 and 200 mg/kg vitamin B3. The depression model was induced with a five days progesterone injection and its discontinuation. In the treated groups, vitamin B3 was injected intraperitoneally. The levels of iron and plasma cortisol in all experimental groups were measured and compared.

Results: the results showed that the cortisol level in the postpartum depression group was significantly increased while the iron level was decreased. In the treated groups, all three doses of vitamin B3 have been shown to decrease cortisol levels and only 50 doses led to the increased iron levels.

Conclusions: In the initial days after childbirth, taking vitamin B3 supplement can lead to reduced cortisol levels and depression in moms, and in order to avoid becoming deficient in iron, it is recommended that all animals take vitamin supplements, which requires further examination.

Keywords: Postpartum depression, Vitamin B3, Cortisol, Iron, Mice.

Introduction

Postpartum depression has been described as a profound episode of experiencing depression during pregnancy or the first 12 months post-partum (Seth et al. 2016). Postpartum depression is a very common phenomenon among women and affects 7-13% of pregnant women and 10 to 15% of women within the six months after childbirth (Brummelte and Galea 2010; Obel et al. 2005). There are some studies on the role of cortisol in depression, especially during pregnancy and postpartum. In the postpartum period or before menstruation, the levels of circulating estrogen and progesterone abruptly lowered; in addition, the risk of minor and major postpartum depression in women with the premenstrual syndrome is higher than other women (Beckley and Finn 2007).

Postpartum depression may be triggered by low levels of the hormone progesterone. In pregnancy, the secretion of female sex hormones estrogen and progesterone increase up to 10 times, but they decrease dramatically after delivery. Abrupt decreases in progesterone after delivery may contribute to the onset of postpartum depression (Beckley and Finn 2007). Recently, the focus was concentrated on balanced effects of neuronal metabolites and progesterone precursors, such as allopregnanolone (Maguire J and I. 2008). These fluctuations are associated with disabling neuropsychiatric disorders including premenstrual syndrome disorder and premenstrual neurological disorder, menstrual migraine, postpartum depression, and anxiety (Backstrom et al. 2003). There has also been a significant positive correlation between postpartum depression with symptoms of depression and cortisol (Lancaster et al. 2010).

In addition, a higher concentration of cortisol level was associated with postpartum depression symptoms in three (Taylor et al. 1994) to five days after childbirth (Okano and Nomura 1992; Seth et al. 2016). Cortisol is a steroid hormone, one of the glucocorticoids, secrete in the cortex of the adrenal glands and is going to be regulated by the hypothalamus-pituitary-adrenal axis (Tsigos and Chrousos 2002).

Typically, in response to a cognitive assessment, corticotrophin-releasing hormone (CRH) is secreted by the paraventricular nucleus (PVN) of the hypothalamus in response to stress and then released into the anterior pituitary. Then CRH stimulates the release of adrenocorticotrophic hormone in the anterior pituitary and this can lead to the release of glucocorticoids, including cortisol from the adrenal cortex (Kammerer et al. 2006). Stress plays an important role in starting and sustaining depression. The Hypothalamic pituitary adrenal axis regulates adrenocortical cortisol response to stimulate the adrenocorticotropic hormone (ACTH) and is secreted during stress (Tsigos and Chrousos 2002). Iron deficiency is thought to be the most common cause of anaemia globally and more than 50% of pregnant women and over 30% of all women suffer from

anemia. Anemia can have devastating effects on the mental health of these women, including cognitive impairment, mood, short-term memory, verbal learning, reduced attention/concentration, intelligence and also leads to depression. Iron deficiency anemia accounts for 95% of total anemia during pregnancy (Goldhaber 2003; Jones and Jellen 2017).

The way and the quality of nutrition are important factors that can influence the behavior. Proper diet helps to maintain homeostasis in the body and environmental factors that can cause a lot of changes in endocrine system of every human. Cortisol is a corticosteroid, in which influence is varied depending on its concentration. Lots of widely available dietary supplements contain nutrients which regulate steroid hormones homeostasis including cortisol (Stachowicz M and A. 2016). Studies have shown that levels of cortisol were higher in those with the lowest levels of vitamins C, B1, B2, B6 and niacin (Diaz et al. 2010).

Vitamin B3, also called niacin, is one of eight water-soluble B vitamins. Niacin also known as nicotinic acid. Other forms of vitamin B3 include the corresponding amide nicotinamide ("niacin amide"). Niacin cannot be directly converted to nicotinamide, but both compounds are precursors of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) in vivo (Viljoen et al. 2015). Niacin does have an antidepressant effect that can be attributed to increased cerebral circulation (Prousky 2010). Adequate intake of niacin and iron converts tryptophan into the compound 5-hydroxy-L-tryptophan which is a homolog of serotonin and reduces depression (Jonathan E and ND. 2010).

The treatment of postpartum depression involves the prevention of iron deficiency, or by eating food sources containing these nutrients or using supplements. (Mischoulon et al. 2000). Therefore, this study aimed to evaluate the effect of intraperitoneal administration of vitamin B3 on iron and plasma cortisol levels in postpartum depression in mature female mice.

Materials and Methods

Animals

This study was conducted at the research department of biology, Islamic Azad University, Izeh Branch in 2017. In this study, 50 adult male NMRI mice aged 6-8 weeks weighing 25-30 g were prepared from the center of animals' maintenance and reproduction of Ahvaz Jundishapur University of Medical Sciences. Animals were randomly divided into 5 groups of 10, including the control group (without taking the drug and or the hormone), the postpartum depression group (progesterone only), and the treatment groups with vitamin B 3 at doses of 50, 100 and 200 mg/kg and kept in standard cages. All animals were kept under controlled temperature conditions of 2 ± 22 ° C and 12 hours of daylight and 12 hours of darkness in lab animal room of Department of Biology. Ethical considerations pertaining to laboratory-based research involving animals were observed in accordance with the instructions given at the university's research and technology department. Furthermore, the mice had access to the compact food provided by Kabileh Shahraza Isfahan Company and water purification system in Izeh city.

Method of postpartum depression

Postpartum depression was administered by intraperitoneal injection of progesterone (5 mg/kg, once a day for 5 days) and then discontinued (Beckley and Finn 2007).

Iron Measurement and Plasma Cortisol

After creating animal models of postpartum depression, the mice in the treatment groups were treated with vitamin B3 (doses of 50, 100 and 200 mg/kg) on the 8th day (three days after the delivery model) and then transferred to the laboratory for surgery and blood collection procedures. After the blood sample has been taken from the heart from 8 to 9 am, Samples were centrifuged for serum separation and serum was prepared to measure iron and plasma cortisol levels. (Seth et al. 2016) and iron levels. In order to measure the iron level in the laboratory, we used the Auto Analyzer Alpha Classic, Pars Azmoon reagent kits, and photometric method (metering mode). In addition, VIDAS-VIDAS and LOT170828 kits and fluorescence methods were used to measure cortisol levels.

Statistical analysis

The data were expressed as mean ± SEM (Standard error mean). The significance level was determined by one-way ANOVA applying LSD's post-hoc test (SPSS, 18). A value of $P < 0.05$ was considered significant.

Results

Figure 1 shows the morning cortisol level in the control group and the group receiving progesterone (postpartum depression) and treatment groups with doses of 50, 100 and 200 mg / g of vitamin B3. Comparing the level of plasma cortisol between control and postpartum depression, Cortisol levels significantly increased in the postpartum depression group ($p <0.001$) and compared with treated groups with B3 vitamin, plasma cortisol level was significantly decreased in doses of 50, 100 ($p <0.001$) and 200 ($p <0.05$), compared with the postpartum depression group. Figure 2 shows the iron level in blood serum in the control group and the group receiving progesterone (postpartum depression) and treated groups in B3 vitamin with doses of 50, 100 and 200. Comparison of iron level in blood serum between the control group and the postpartum depression group indicated a decrease in blood serum level of iron in the postpartum depression group compared to the control group ($p <0.01$). Similarly, the comparison of iron level in blood serum between treated groups with B vitamin at doses of 50, 100 and 200 indicated that a dose of 50 ($p <0.05$) only showed an increase in iron level in blood serum in comparison with the group receiving progesterone (postpartum depression).

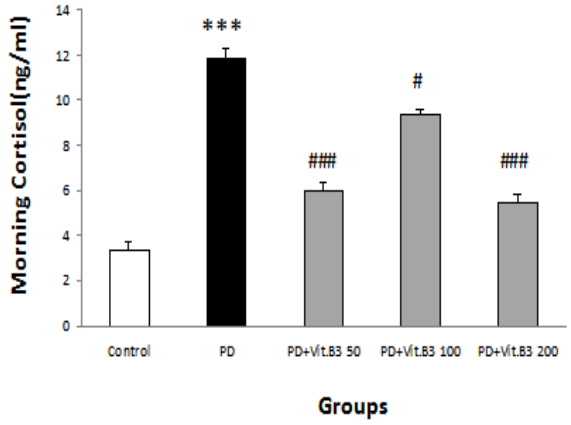

Figure 1: Comparison Mean ± SEM Plasma cortisol level (ng/ml) between control group, postpartum depression (PD) and PD group treated with doses of 50,100 and 200 mg/kg of B3 vitamin. * shows significance between the control group and PD. # shows significant difference between PD and treated groups.

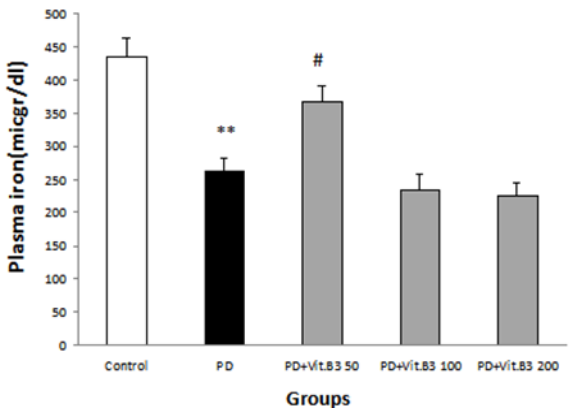

Figure 2: Comparison Mean ± SEM of iron level between control group, postpartum depression (PD) and PD group treated with B3 vitamin at doses of 50, 100 and 200 mg/kg. * shows significance between the control group and PD. # shows significant difference between PD and treated groups.

Discussion

The findings of this study showed that plasma cortisol level increased in postpartum depression group, but using different doses of vitamin B3 caused a significant decrease in plasma cortisol and administration of 50mg/kg vitamin B3 in depressed mice resulted in an increase in plasma iron levels. Anxiety and depression are common disorders in pregnancy, postpartum and after childbirth; some women may be recovered and some may stay in that state their whole lives. Therefore, identification of any biological agent that influences this incidence seems important. A wide variety of factors can be attributed to this phenomenon including hormonal fluctuations during pregnancy and postpartum (estrogen and progesterone), as well as corticotrophin-releasing hormone (CRH) and increased cortisol (Kammerer et al. 2006).

The results of our study showed that the cortisol level in the postpartum depression group was significantly increased while the iron level was decreased. In the treated groups, all three doses of vitamin B3 have been shown to decrease cortisol levels but only 50 doses led to increased iron levels. Studies suggest an association between anemia and depression disorders (Rao et al. 2008). Recent studies have shown that symptoms of postpartum depression are frequently reported among women with anemia than non-anemic women (Rao et al. 2008).

Several trace elements such as zinc, manganese, and iron are transmitted to the adult brain and are probably the required components for neural function. Anemia can have devastating effects on the mental health of these women, including cognitive impairment, mood, short-term memory, verbal learning, reduced attention/concentration, intelligence and also leads to depression as well as an increase in cortisol levels is associated with a decrease in plasma iron levels (Diaz et al. 2010). In animal models, cortisol concentrations have been observed significantly higher during the ovarian activity in the post-partum period in cows (Ezzat Ahmed A et al. 2013). Elevated cortisol levels have been reported in the study by Nairoop et al. (2006) and they showed that cortisol levels were significantly higher in the group with postpartum depression (Nierop et al. 2006). In women with postpartum depression symptoms, postpartum cortisol level was shown higher implying an altered response to HPA axis in postpartum depression (Iliadis et al. 2015). Increased level of cortisol can decrease the secretions of the hypothalamus and the pituitary gland in negative feedback loop to suppress CRH production. However, in depressed patients, the weakened negative feedback loop leads to excessive production of CRH; consequently, simultaneously with increased stress, cortisol causes changes in the immune system and increased production of cytokines. There is a negative feedback loop between the HPA axis and the immune system. Cytokines stimulate the HPA-axis and cause excess cortisol secretion (Capello and Markus 2014; Iliadis et al. 2015).

Regarding amino acid supplements like tryptophan with serotonin itself, its precursor, can reduce exercise-induced cortisol levels (Bochem et al. 2013). Further, the adrenal hormone cortisol, which is produced in response to stress, converts tryptophan into a chemical called kynurenine, which cannot be converted into serotonin. Serotonin is one of the active neurotransmitters in the central nervous system which is found mostly in the digestive system. As a natural anti-depressant, serotonin level in the brain causes feelings of joy and euphoria. Lowered levels of serotonin causes increased depression, anxiety, migraine pain, high blood pressure and insomnia. Moreover, all steroid hormones, including those produced by the adrenal cortex with low-density lipoprotein (LDL) can synthesize and gain enter extracellular cortex cells through the endocytosis process and eventually be released via cholesterol cell lysosomes. ACTH increases the volume of the adrenal glands for LDL and cholesterol separation. Cholesterol enters the mitochondria and breaks down into pregnenolone by the enzyme cholesterol dismutase in the intestine, then converts into a 17α-hydroxypreg by 17 α-hydroxyl's enzymes, then to enzyme 3 beta-hydroxysteroid dehydrogenates, and then converts into 11-deoxycortisol via 21-hydroxylase enzyme and eventually converts into cortisol by means of enzyme 11β-hydroxysteroid dehydrogenize (Scott et al. 2012). Both forms of vitamin B3 include the corresponding amide and nicotinamide ("niacin amide"), where the carboxyl group has been replaced by a

carboxamide group (CONH). Both forms are in the form of NAD in the body and NADP, NAD plays a role of the coenzyme. Even though vitamin B3's mechanisms of action have not been substantiated from rigorous controlled clinical trials, it does appear to have beneficial effect upon depression. Oral niacin is believed to increase cerebral blood flow and decrease depression. Intravenous niacin has some supportive data demonstrating that it might increase cerebral blood flow, but data on oral niacin and cerebral hemodynamics is lacking (Prousky 2010).

Niacin amide in combination with tryptophan has more robust data demonstrating an effective antidepressant response among patients with unipolar depression. The niacin amide-tryptophan combination increases serotonin levels within the brain, but niacin amide by itself might possess antidepressant effect. It is imperative that properly designed and well conducted controlled trials are developed in order to determine the true therapeutic effects and adverse effect profile of niacin and niacin amide for depression (Prousky 2010). Some studies have found that niacin amide is an important compound which is able to inhibit 11beta-hydroxysteroid dehydrogenize types 1 enzyme. As a result, it inhibits the synthesis of cortisol and increases its inactive form. Additionally, niacin amide enhances the 11beta-hydroxysteroid dehydrogenase types II enzyme that catalyzes the intracellular transformation of glucocorticoid into its inactive metabolite (Altschul et al. 1955).

Two isoenzymes have been identified; 11beta-hydroxysteroid dehydrogenase types1 enzyme acts predominantly as an oxidoreductase enzyme in the body and NADPH is used as a cofactor for the production of cortisol. However, 11 beta-hydroxysteroid dehydrogenize types II enzyme acts exclusively as a NAD-dependent dehydrogenize which inactivates cortisol by converting it to cortisone (Altschul et al. 1955). It was initially reported in 1955 that nicotinic acid (niacin) lowered cholesterol levels in normal subjects as well as in patients with hypercholesterolemia. There have been many subsequent studies that have supported niacin as a broad-spectrum lipid-regulating medication. Niacin reduces total cholesterol, triglycerides, VLDL-C, LDL-C and lipoprotein (a) (Lp[a]) levels, in addition to increasing HDL-C levels (Carlson 2005).

Furthermore, in an in vitro system, niacin has been shown to have antioxidant and anti-inflammatory properties. This is mediated by increases in NADP, reductions in glutathione levels and inhibition of the following: angiotensin II-induced reactive oxygen species production; LDL-C oxidation (Kamanna and Kashyap 2008). According to the results of the past, vitamin B3, or niacin, also reduces the synthesis of cortisol by lowering the lipid profiles resulting in increasing the pathway for serotonin synthesis. It also reduces depression along with increased brain circulation; all these results are consistent with those of the current study. In our study, vitamin B3 was able to significantly reduce the level of cortisol in the animal model of postpartum depression and a dose of 50 increased iron levels. Based on the findings of this study, for more detailed examination, it is suggested that anemia and non-anemic states of the samples be evaluated prior to the administration of the vitamin and then, various doses of vitamin B3 are tested on anemia and non-anemic groups, as well as the long-term use of vitamin B3.

Acknowledgments

The authors would like to thank the Research Deputy of Islamic Azad University, Izeh Branch for its support to carry out this study. This article was extracted from Mrs. Marzieh Abin, M.Sc. thesis. This project was financially supported by the student herself.

Conflict of Interest

The authors declared no conflicts of interest**.**

References

1. Altschul R, Hoffer A, and Stephen JD. 1955. Influence of nicotinic acid on serum cholesterol in man. Archives of biochemistry and biophysics 54(2):558-559.
2. Backstrom T, Andersson A, Andree L, Birzniece V, Bixo M, Bjorn I, Haage D, Isaksson M, Johansson IM, Lindblad C et al. . 2003. Pathogenesis in menstrual cycle-linked CNS disorders. Annals of the New York Academy of Sciences 1007:42-53.
3. Beckley EH, and Finn DA. 2007. Inhibition of progesterone metabolism mimics the effect of progesterone withdrawal on forced swim test immobility. Pharmacology, biochemistry, and behavior 87(4):412-419.
4. Bochem AE, Holleboom AG, Romijn JA, Hoekstra M, Dallinga-Thie GM, Motazacker MM, Hovingh GK, Kuivenhoven JA, and Stroes ES. 2013. High density lipoprotein as a source of cholesterol for adrenal steroidogenesis: a study in individuals with low plasma HDL-C. Journal of lipid research 54(6):1698-1704.
5. Brummelte S, and Galea LA. 2010. Depression during pregnancy and postpartum: contribution of stress and ovarian hormones. Progress in neuro-psychopharmacology & biological psychiatry 34(5):766-776.
6. Capello AE, and Markus CR. 2014. Effect of sub chronic tryptophan supplementation on stress-induced cortisol and appetite in subjects differing in 5-HTTLPR genotype and trait neuroticism. Psychoneuroendocrinology 45:96-107.
7. Carlson LA. 2005. Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. Journal of internal medicine 258(2):94-114.
8. Diaz E, Ruiz F, Hoyos I, Zubero J, Gravina L, Gil J, Irazusta J, and Gil SM. 2010. Cell damage, antioxidant status, and cortisol levels related to nutrition in ski mountaineering during a two-day race. Journal of sports science & medicine 9(2):338-346.
9. Ezzat Ahmed A, Ismail M.N, Aref MS, Zain El-Abedin A, and A.Y. K. 2013. Cortisol and Postpartum Luteal Function in Cattle. Iranian Journal of Applied Animal Science 3(3):465-470.
10. Goldhaber SB. 2003. Trace element risk assessment: essentiality vs. toxicity. Regulatory toxicology and pharmacology : RTP 38(2):232-242.
11. Iliadis SI, Comasco E, Sylven S, Hellgren C, Sundstrom Poromaa I, and Skalkidou A. 2015. Prenatal and Postpartum Evening Salivary Cortisol Levels in Association with Peripartum Depressive Symptoms. PloS one 10(8):e0135471.

12.Jonathan E, and ND. P. 2010. Vitamin B3 for Depression: Case Report and Review of the Literature. Journal of Orthomolecular Medicine 25(3):137-143.
13.Jones BC, and Jellen LC. 2017. Systems Genetics Analysis of Iron and Its Regulation in Brain and Periphery. Methods in molecular biology 1488:467-480.
14.Kamanna VS, and Kashyap ML. 2008. Mechanism of action of niacin. The American journal of cardiology 101(8A):20B-26B.
15.Kammerer M, Taylor A, and Glover V. 2006. The HPA axis and perinatal depression: a hypothesis. Archives of women's mental health 9(4):187-196.
16.Lancaster CA, Gold KJ, Flynn HA, Yoo H, Marcus SM, and Davis MM. 2010. Risk factors for depressive symptoms during pregnancy: a systematic review. American journal of obstetrics and gynecology 202(1):5-14.
17.Maguire J, and I. M. 2008. GABAAR Plasticity during Pregnancy: Relevance to Postpartum Depression. Neuron 59(2):207-213.
18.Mischoulon D, Burger JK, Spillmann MK, Worthington JJ, Fava M, and Alpert JE. 2000. Anemia and macrocytosis in the prediction of serum folate and vitamin B12 status, and treatment outcome in major depression. Journal of psychosomatic research 49(3):183-187.
19.Nierop A, Bratsikas A, Zimmermann R, and Ehlert U. 2006. Are stress-induced cortisol changes during pregnancy associated with postpartum depressive symptoms? Psychosomatic medicine 68(6):931-937.
20.Obel C, Hedegaard M, Henriksen TB, Secher NJ, Olsen J, and Levine S. 2005. Stress and salivary cortisol during pregnancy. Psychoneuroendocrinology 30(7):647-656.
21.Okano T, and Nomura J. 1992. Endocrine study of the maternity blues. Progress in neuro-psychopharmacology & biological psychiatry 16(6):921-932.
22.Prousky J. 2010. Vitamin B3 for depression: Case report and review of the literature. 137-147 p.
23.Rao TS, Asha MR, Ramesh BN, and Rao KS. 2008. Understanding nutrition, depression and mental illnesses. Indian journal of psychiatry 50(2):77-82.
24.Scott JS, Bowker SS, Deschoolmeester J, Gerhardt S, Hargreaves D, Kilgour E, Lloyd A, Mayers RM, McCoull W, Newcombe NJ et al. . 2012. Discovery of a potent, selective, and orally bioavailable acidic 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) inhibitor: discovery of 2-[(3S)-1-[5-(cyclohexylcarbamoyl)-6-propylsulfanylpyridin-2-yl]-3-piperidyl]acet ic acid (AZD4017). Journal of medicinal chemistry 55(12):5951-5964.
25.Seth S, Lewis AJ, and Galbally M. 2016. Perinatal maternal depression and cortisol function in pregnancy and the postpartum period: a systematic literature review. BMC pregnancy and childbirth 16(1):124-142
26.Stachowicz M, and A. L. 2016. The effect of diet components on the level of cortisol. European Food Research and Technology 242(12): 2001–2009.
27.Taylor A, Littlewood J, Adams D, Dore C, and Glover V. 1994. Serum cortisol levels are related to moods of elation and dysphoria in new mothers. Psychiatry research 54(3):241-247.
28.Tsigos C, and Chrousos GP. 2002. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. Journal of psychosomatic research 53(4):865-871.
29.Viljoen M, Swanepoel A, and Bipath P. 2015. Antidepressants may lead to a decrease in niacin and NAD in patients with poor dietary intake. Medical hypotheses 84(3):178-182