ORIGINAL RESEARCH PAPER

Volume-7 | Issue-10 | October-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

FOLIC ACID AND VITAMIN B12 IN TREATMENT OF ALZHEIMER'S DISEASE, DIABETES AND OF HIGH CORTISOL LEVELS

Medical Science

Mr. Amos Gelbard Zefat Academic College, Zefat, Israel

ABSTRACT

Background: This article aims to explain the process in which Cortisol, known as the "Stress Hormone", designated to allow the transfer of glucose from the body to the blood stream to respond to stressful situations, is the cause for several key illnesses, among them Alzheimer's Disease and Diabetes, hypertension and schizophrenia.

This study will use past literature and connect the dots regarding the mechanism in which these illnesses work and explain why the way to downgrade cortisol levels and therefore to possibly prevent or even cure these diseases, is by absorption of vitamin B12 and Folic acid through nutrition or food supplementation.

Through analysis of previously researched literature this study will reach conclusions not previously discussed. It will use previous essays and researches to support its theory and take them a step further to thoroughly explain the mechanisms and possible therapeutic strategies deriving from them.

Methods: The research relies on theory and analysis based on multiple previous studies referenced and quoted

Results: In AD, Diabetes and Hypertension high cortisol levels correlate with low folate and vitamin b12 levels and with high homeocysteine levels.

Conclusions: A preventive and a possible treatment to AD and Diabetes as well as to other diseases explained is by consumption of folic acid and viamin b12

KEYWORDS

Cortisol, Alzheimer's disease, Diabetes, Folic Acid, Folate, Vitamin B12

BACKGROUND

In previous articles, I studied the role of Cortisol, the "Stress Hormone" - produced to promote transfusion of sugar to the bloodstream in stressful situations - as the possible cause for Alzheimer's disease. This is based on the deteriorating effect Cortisol has on alpha, beta and gamma secretase, enzymes in charge of the peptide of amyloid beta [15-20, 1].

Alzheimer's disease is defined by accumulation of beta amyloid plaques within the neurons of the brain.[15] The enzymes responsible for the peptide of amyloid beta and accordingly of this malfunction are called alpha, beta and gamma secretases.[16] The deterioration of their activity possibly stems from excessive levels of cortisol secretion through long periods of time as is evident in Alzheimer's Disease[17-20]

Cortisol, "The Stress Hormone" is produced by the brain to promote transfer of sugar to the bloodstream in "fight or flight" situations.

I first hypothesized that one way to downplay Cortisol secretion is by elevating of blood glucose levels through nutrition and therefore compensate for the need in Cortisol [1], if you maintain high blood glucose levels, the need for Cortisol subsides, but this was challenged by Alzheimer's occurrence in Type2 Diabetes Patients. [25- 26, 21, 5, 2]

I then reached a conclusion that diabetes could be a behavioral reaction to high Cortisol levels, for the same logic of answering Cortisol secretion with Glucose [1], I realized that my initial idea of answering high cortisol secretion with glucose consumption could be the underlying cause for Diabetes.

As I tried to think what could cure high Cortisol Levels, not by duplication of its role, but by itself, I found numerous studies that show low folate (folic acid) levels and not just high cortisol levels to directly correlate with Alzheimer's, Higher Folate intake to reduce risk of Alzheimer's and Folic Acid treatment to manufacture improvement on all important parameters in AD patients.[6- 28-29,10]

I realized this may be also true for Cushing Syndrome [11] and Schizophrenia [12], where high cortisol levels and low folate levels are evidenced [11-12]. And also for Diabetes as high Cortisol levels are indeed related to the development of Diabetes and Folate Treatment proved beneficial in Diabetics [26-23,13-14,5].

Low vitamin B12 Levels also proved to correlate with these conditions [7, 12, 27-29, 31, 35-37].

These conditions also correlate with high Homocysteine levels and diseases deriving from it [7, 11-12, 30-32, 35, 37-38], and with high blood pressure (Hypertension) [38,33-36,29].

If high Cortisol levels indeed correlate with low folate and vitamin B12 levels, it's sensible to suggest that excessive cortisol secretion relies on insufficient Folate and Vitamin B12 consumption and that treatment and prevention of all these diseases and all diseases deriving from high Cortisol could be by improving consumption of folic acid and vitamin b12.

RESULTS

Alzheimer's disease is defined by accumulation of beta amyloid plaques within the neurons of the brain.[15] Alzheimer's disease (AD) pathogenesis is widely believed to be driven by the production and deposition of the β-amyloid peptide (Aβ). For many years, investigators have been puzzled by the weak to nonexistent correlation between the amount of neuritic plaque pathology in the human brain and the degree of clinical dementia. Substantial evidence now indicates that the solubility of Aβ, and the quantity of Aβ in different pools, may be more closely related to disease state.[15] The enzymes responsible for the peptide of amyloid beta and accordingly of this malfunction are called alpha, beta and gamma secretases.[16] Generation of Amyloid peptide (Abeta) is at the beginning of a cascade that leads to Alzheimer's disease. Currenty, the mechanisms of Abeta generation and Abeta prevention are subject of intensive research. Amyloid precursor protein (APP), as well as beta- and gamma-secretases are the principal players involved in Abeta production, while alpha-secretase cleavage on APP prevents Abeta deposition. [16] These proteases that are involved in the processing of amyloid precursor protein-alpha-secretase, beta-secretase and gamma-secretase-are of particular interest as they are central to the generation and modulation of amyloid-beta peptide. [17] physical and psychosocial stressors, in part acting through the hypothalamic-pituitary-adrenal (HPA) axis, may accelerate the process of Alzheimer's disease (AD) [18], Higher HPA activity, as reflected by increased plasma cortisol levels, is associated with more rapid disease progression in subjects with Alzheimer-type dementia[19]. Another study found "Increased cortisol levels in aging and Alzheimer's disease in postmortem cerebrospinal fluid". [20]

In type 2 diabetic subjects, hypothalmic-pituitary-adrenal activity is enhanced in patients with diabetes complications and the degree of cortisol secretion is related to the presence and number of diabetes complications.[5] Epidemiological and biological evidences support a link between type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD). Persons with diabetes have a higher incidence of cognitive decline and an increased risk of developing all types of dementia. Cognitive deficits in persons with diabetes mainly affect the areas of psychomotor efficiency, attention, learning and memory, mental flexibility and speed, and executive function. Increased cortical and subcortical atrophy have been evidenced after controlling for diabetic vascular disease and inadequate cerebral circulation. Disturbances in brain insulin signaling mechanisms may contribute to the molecular, biochemical, and

histopathological lesions in AD. [21] Type 2 Diabetes increases the risk of dementia more than 2-fold. [25] Late-night salivary Cortisol (LNSC) is reportedly highly accurate for the diagnosis of Cushing's syndrome (CS). The purpose of this study was to evaluate LNSC levels in elderly male veterans with and without diabetes [26]. Average Late-night salivary Cortisol levels (nmol/l) in diabetics were significantly higher than in nondiabetics [median (interquartile range): 2·6 (1·8–4·1) *vs*.1·6 (1·0–2·0)] and in those aged ≥ 60 compared to < 60 [2·7 (2·0–4·3) *vs*. 1·9 (1·4–2·9)]. [26]

High cortisol and low folate are the only routine blood tests predicting probable Alzheimer's disease after age 75[6], Serum total homocysteine levels were significantly higher and serum folate and vitamin B12levels were lower in patients with dementia of Alzheimer type and patients with histologically confirmed AD than in controls Low blood levels of folate and vitamin B12, and elevated homocysteine (tHcy) levels were associated with AD.[7] Low blood folate and raised homocysteine concentrations are associated with poor cognitive function. Folic acid supplementation improves cognitive function. [8] This small pilot study examined the effect of folic acid supplementation on newly diagnosed patients with AD. Folic acid improved cognition and markers of inflammation. [9] Study findings have suggested an association between Alzheimer's disease (AD) risk and several vitamins and have speculated about their use as preventive agents. Here, we examine whether total intake (intake from diet plus supplements) of antioxidant vitamins (E, C, carotenoids) and B vitamins (folate, B6, and B12) is associated with a reduced risk of AD…After a mean follow-up of 9.3 years, AD developed in 57 participants. Higher intake of folate (RR, 0.41; 95% confidence interval [CI], 0.22 to 0.76), vitamin E (RR, 0.56; 95% CI, 0.30 to 1.06), and vitamin B6 (RR, 0.41; 95% CI, 0.20 to 0.84) were associated individually with a decreased risk of AD after adjusting for age, gender, education, and caloric intake. When these 3 vitamins were analyzed together, only total intake of folate at or above the RDA (RR, 0.45; 95% CI, 0.21 to 0.97) was associated with a significant decreased risk of AD. No association was found between total intake of vitamins C, carotenoids, or vitamin B12 and risk of AD.[10]

This study's objective was to explore the associations of low serum levels of vitamin B12 and folate with AD occurrence. When using B12 ≤150pmol/L and folate ≤10 nmol/L to define low levels, compared with people with normal levels of both vitamins, subjects with low levels of B12 or folate had twice higher risks of developing AD (relative risk [RR] = 2.1, 95% CI = 1.2 to 3.5). These associations were even stronger in subjects with good baseline cognition (RR = 3.1, 95% CI = 1.1 to 8.4). Similar relative risks of AD were found in subjects with low levels of B12 or folate and among those with both vitamins at low levels. [28]

I realized this may be also true for Cushing Syndrome [11] and Schizophrenia [12], where high cortisol levels and low folate levels are evidenced [11-12].

In Cushing Syndrome, active hypercortisolism is associated with hyperhomocysteinemia and reduced serum folate concentrations,[11] And the 2md study showed Reduced folic acid, vitamin B12 and docosahexaenoic acid and increased homocysteine and cortisol in never-medicated schizophrenia patients. [12]

In type 2 diabetic subjects, hypothalmic-pituitary-adrenal activity is enhanced in patients with diabetes complications and the degree of cortisol secretion is related to the presence and number of diabetes complications.[5] Short-term oral folic acid supplementation significantly enhances endothelial function in type 2 diabetic patients. [13] Data imply that folate can be used to improve nitric oxide status and to restore endothelial dysfunction in patients with Type II diabetes. Our results provide a strong rationale for the initiation of studies that investigate whether supplementation with folic acid prevents future cardiovascular events in this patient group. [14] Average Late-night salivary cortisol levels (nmol/l) in diabetics were significantly higher than in non-diabetics. [26]

Low vitamin B12 Levels also proved to correlate with these conditions [7, 12, 27-29, 31, 35-37] Low blood levels of folate and vitamin B12, and elevated tHcy levels were associated with AD. [7] Significantly lower levels of folate and vitamin B12 in plasma and folate in red blood cells were observed in first-episode psychotic patients compared to healthy controls.[12] Vitamin B12 levels in the serum and the cerebrospinal fluid (CSF) were significantly lower in the AD group than in the multi-infarct dementia group.[27] When using B12 ≤150pmol/L and folate ≤10 nmol/L to define low levels, compared with people with normal levels of both vitamins, subjects with low levels of B12 or folate had twice higher risks of developing AD. [28] Key constituents of one carbon cycle (folic acid, vitamin B12 and DHA) may play a role in reducing oxidative stress and inflammation in pregnancy induced hypertension. [29] Low intakes of folic acid and vitamin B12, and hyperhomocysteinemia, in both the healthy population living in urban slums and adjacent urban non-slum areas, are important observations. [31] In all 3 patient groups (Type2 Diabetes, Hypertension, Cardiov ascular disease) Elevated levels of vitamin D2 and homocysteine were observed, whereas the levels of folic acid and vitamins D3 and B12 were lower than the reference range for each serum marker. [35] The data suggest that high intakes of folic acid and vitamin B12 are associated with lower levels of blood pressure among preschool children. [36] This finding suggests that a fortification policy based on folic acid and vitamin B12, rather than folic acid alone, is likely to be much more effective at lowering of Homocysteine concentrations, with potential benefits for reduction of risk of vascular disease. [37]

These conditions also correlate with high Homocysteine (Hcy) levels and diseases deriving from it [7, 11-12, 30-32, 35, 37-38].

Serum tHcy levels were significantly higher and serum folate and vitamin B12 levels were lower in patients with dementia of Alzheimer type and patients with histologically confirmed AD than in controls [7], homocysteine levels were significantly associated with midnight serum cortisol levels, which is the most sensitive marker of endogenous hypercortisolism, and serum folate levels [11], Reduced folic acid, vitamin B12 and docosahexaenoic acid and increased homocysteine and cortisol in never-medicated schizophrenia patients [12] Hyperhomo cysteinemia occurred with significantly greater frequency (seven of 18, 39%) in patients with non-insulin-dependent diabetes mellitus as compared with age-matched controls (7%) [30] Low intakes of folic acid and vitamin B12, and hyperhomocysteinemia, in both the healthy population living in urban slums and adjacent urban non-slum areas [31] Cereal fortified with folic acid has the potential to increase plasma folic acid levels and reduce plasma homocysteine levels [32] In all 3 patient groups, elevated levels of vitamin D2 and homocysteine were observed, whereas the levels of folic acid and vitamins D3 and B12 were lower than the reference range for each serum marker [35] This finding suggests that a fortification policy based on folic acid and vitamin B12, rather than folic acid alone, is likely to be much more effective at lowering of homocysteine concentrations [37] Patients with the metabolic syndrome had significantly higher plasma Hcy levels. After correction for covariates, increasing Hcy levels were associated with an increasing prevalence of the metabolic syndrome, coronary heart disease, and CVD. Plasma Hcy was directly correlated with age, waist circumference, fasting glucose, triglyceride, uric acid, and fibrinogen levels, and homeostatic model assessment index and inversely with creatinine clearance and high-density lipoprotein cholesterol, vitamin B12, and folate levels [38] and with high blood pressure (Hypertension) [29, 33-36, 38]:

A combined supplementation of omega-3 fatty acids and micronutrients (folic acid, vitamin B12) reduces oxidative stress markers in a rat model of pregnancy induced hypertension. [29] There is emerging evidence that cortisol plays a significantly greater role in human hypertension than previously thought [33], Oral cortisol increases blood pressure in a dose-dependent fashion. At a dose of 80-200 mg/day, the peak increases in systolic pressure are of the order of 15 mmHg. [34] Folic Acid and Vitamins D and B12 Correlate With Homocysteine in Chinese Patients With Type-2 Diabetes Mellitus, Hypertension, or Cardiovascular Disease [35] and Dietary intake of vitamin B12 and folic acid is associated with lower blood pressure in Japanese preschool children.[36] Elevated plasma Homocysteine is associated with the metabolic syndrome in hypertensive patients. Prevalence of events increases with increasing plasma Homocysteine levels suggesting a contribution of Hcy to cerebro-cardiovascular diseases in these patients.[38]

CONCLUSIONS

Alzheimer's disease but also Diabetes, Cushing Syndrome, Schizophrenia, Hypertension, High Homocysteine levels and possibly other physical and mental illnesses, stem from or are characterized by elevated Cortisol Secretion. The low levels of Folic Acid and Vitamin B12 evidenced in these diseases could lead to establishing a link between elevated cortisol levels and insufficient folate and B12 consumption.

Based on this analysis of the below referenced studies and clinical data, a preventive and a possible treatment to these diseases and symptoms and to diseases deriving from them, should be by nutritional consumption of more folic acid and B12 or by food supplementation of these substances.

It is important for these findings to be researched further, in prevention but also for their potential as treatment.

Declarations:
Ethics approval and consent to participate:
Not applicable

Consent for publication:
Not applicable

Availability of data and material:
Not applicable

Competing interests:
There are no competing interests

Funding:
I received no funding for my work

Authors' contributions:
I'm the only author

ACKNOWLEDGEMENTS:
I would like to thank my family, friends, everyone supporting me and helping me out

REFERENCES

1. Amos Gelbard. 'Glucose Role in Treatment of Alzheimer's Disease'. Zefat Academic College, Zefat, Israel. 2016 https://www.omicsonline.org/open-access/glucose-role-in-treatment-of-alzheimers-disease-2167-7182-1000334.php?aid=77735
2. Amos Gelbard. 'Rethinking Glucose role in treatment of Alzheimer's Disease based on the disease incidence in Diabetes type2 Patients'. Zefat Adademic College, Zefat, Israel. 2017 https://www.omicsonline.org/open-access/rethinking-glucose-role-in-alzheimers-disease-basedon-the-disease-incidencein-diabetes-type-2-patients-2167-7182-1000414.php?aid=88104
3. Amos Gelbard. 'Cortisol and Folate and their Roles in Alzheimer's Disease, Diabetes'. Zefat Adademic College, Zefat, Israel. 2017 http://scientonline.org/open-access/cortisol-and-folate-and-their-roles-in-alzheimers-disease-diabetes.pdf
4. Amos Gelbard. 'Discussion about Insulin Role in Diabetes Treatment'. Zefat Adademic College, Zefat, Israel. 2017 http://medwinpublishers.org/DOIJ/DOIJ16000161.pdf
5. Iacopo Chiodini, Guido Adda, Alfredo Scillitani, Francesca Coletti, Valentina Morelli, Sergio Di Lembo, Paolo Epaminonda, Benedetta Masserini, Paolo Beck-Peccoz, Emanuela Orsi, Bruno Ambrosi and Maura Arosio. 'Cortisol Secretion in Patients with Type 2 Diabetes: Relationship with chronic complications'. Milan, Italy. 2007 http://care.diabetesjournals.org/content/30/1/83
6. Hinterberger M, Zehetmayer S, Jungwirth S, Huber K, Krugluger W, Leitha T, Krampla W, Tragl KH, Fischer P. 'High cortisol and low folate are the only routine blood tests predicting probable Alzheimer's disease after age 75-results of the Vienna Transdanube Aging Study.' Vienna, Austria. 2013 https://www.ncbi.nlm.nih.gov/pubmed/23581921
7. Robert Clarke, MD; A. David Smith, DPhil; Kim A. Jobst. 'Folate, Vitamin B12, and Serum Total Homocysteine Levels in Confirmed Alzheimer Disease'. Oxford, England; Bergen, Norway. 1998 http:// jamanetwork .com/journals /jamaneurology/ fullarticle/ 774437
8. Undurti N.Das. 'Folic acid and polyunsaturated fatty acids improve cognitive function and prevent depression, dementia, and Alzheimer's disease—But how and why?'. Ohio, USA. 2007 http://www.sciencedirect.com/science/article/pii/S0952327807001354
9. Hui Chen, Shuai Liu, Lu Ji, Tianfeng Wu, Yong Ji, Yuying Zhou, Miaoyan Zheng, Meilin Zhang, Weili Xu, and Guowei Huang. 'Folic Acid Supplementation Mitigates Alzheimer's Disease by Reducing Inflammation: A Randomized Controlled Trial'. China. 2016 https://www.hindawi.com/journals/mi/2016/5912146
10. María M. Corrada, Claudia H. Kawas, Judith Hallfrisch, Denis Muller and Ron Brookmeyere. 'Reduced risk of Alzheimer's disease with high folate intake: The Baltimore Longitudinal Study of Aging'. Maryland, California; USA. 2005 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3375831
11. Terzolo M, Allasino B, Bosio S, Brusa E, Daffara F, Ventura M, Aroasio E, Sacchetto G, Reimondo G, Angeli A, Camaschella C. 'Hyperhomocysteinemia in patients with Cushing's syndrome.' Torino, Italy. 2004 https:// www. ncbi. nlm.nih .gov /pubmed/ 15292300
12. Anvita Kalea, Nilesh Naphadeb, Swati Sapkaleb, Marellasv Kamarajub, Anilkumar Pillaic, Sadhana Joshia, Sahebarao Mahadik. 'Reduced folic acid, vitamin B12 and docosahexaenoic acid and increased homocysteine and cortisol in never-medicated schizophrenia patients: Implications for altered one-carbon metabolism'. USA; India. 2009 www.sciencedirect.com/science/article/pii/S0165178109000225
13. Arduino A. Mangoni, Roy A. Sherwood, Belinda Asonganyi, Cameron G. Swift, Stephen Thomas, Stephen H.D. Jackson. 'Short-Term oral folic acid supplementation enhances endothelial function in patients with type 2 diabetes'. American Journal of Hypertension. 2005https://academic.oup.com/ajh/article/18/2/220/121871/Short-Term-oral-folic-acid-supplementation
14. R. van Etten; de Koning, E; Verhaar, M; Gaillard, C; Rabelink, T. 'Impaired NO-dependent vasodilation in patients with Type II (non-insulin-dependent) diabetes mellitus is restored by acute administration of folate'. Utrecht, The Netherlands. 2002 https://elibrary.ru/item.asp?id=1362020
15. M. Paul Murphy and Harry LeVine, III. 'Alzheimer's Disease and the β-Amyloid Peptide'. Kentucky, USA. 2010 https:// www .ncbi .nlm.nih. gov/ pmc/ articles/ PMC2813509/
16. Epis R, Marcello E, Gardoni F, Di Luca M. 'Alpha, beta-and gamma-secretases in Alzheimer's disease.' Milano, Italy. 2012 https: //www. ncbi. nlm. nih.gov/ pubmed/ 222 02113
17. Strooper BD, Vassar R, Golde T. 'The secretases: enzymes with therapeutic potential in Alzheimer disease.' Nat Rev Neurol 6: 99-107. Leuven, Belgium. 2010 https:// www. ncbi.nlm.nih.gov/pubmed/20139999
18. Dong H, Csernansky. 'Effects of Stress and Stress Hormones on Amyloid¬β Protein and Plaque Deposition'. J Alzheimers Dis 18: 459-469. Chicago, USA. 2009 https:// www. ncbi.nlm.nih.gov/pubmed/19584430
19. Csernansky JG, Dong H, Fagan AM, Wang L, Xiong C, et al, 'Plasma cortisol and progression of dementia in subjects with Alzheimer ¬type dementia'. Am J Psychiatry 163: 2164-2169. St. Louis, USA. 2006 https:// www. ncbi. nlm. nih. gov/ pubmed/ 17151169
20. Swaab DF, Raadsheer FC, Endert E, Hofman MA, Kamphorst W, et al. 'Increased cortisol levels in aging and Alzheimer's disease in postmortem cerebrospinal fluid.' J Neuroendocrinol 130: 1707-1712. Amsterdam, The Netherlands. 1994. https:// www.ncbi.nlm.nih.gov/pubmed/7894471
21. Mario Barbagallo and Ligia J Dominguez. 'Type 2 diabetes mellitus and Alzheimer's disease'. Palermo, Italy. 2014 https:// www. ncbi. nlm. nih. gov /pmc /articles /PMC 4265876
22. Gejl M, Gjedde A, Egefjord L, Moller A, Soren B, et al. 'In Alzheimer's Disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: Randomized, placebo-controlled, double-blind clinical trial'. Aging Neurosci 8: 108. Denmark. 2016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4877513
23. Bak AM, Egefjord L, Gejl M, Steffensen C, Stecher CW, et al. 'Targeting amyloid-beta by glucagon-like peptide-1 (GLP-1) in Alzheimer's disease and diabetes'. Aarhus, Denmark. 2011 https:// www. researchgate .net/ publication/ 51485800 Targeting amyloid-beta_by_glucagon-like_peptide_-1_GLP-1_in_ Alzheimer's_ disease_and_ diabetes
24. VA, H ölscher C. 'GLP-1 agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid'. Eur J Pharmacol 587: 112-117. Northern Ireland, United Kingdom. 2006 https://www.ncbi.nlm.nih.gov/pubmed/18466898
25. Hsu, Chih-Cheng;, Wahlqvist, Mark L. Lee, Meei-Shyuan Tsai, Hsin-Ni. 'Incidence of Dementia is increased in Type 2 Diabetes and Reduced by the Use of Sulfonylureas and Metformin'. Zhunan, Tawiwan. 2010 http://content.iospress.com/articles/journal-of-alzheimers-disease/jad101524
26. Hau Liu, Dena M. Bravata, Josel Cabaccan, Hershel Raff, Elisabeth Ryzen. 'Elevated late-night salivary cortisol levels in elderly male type 2 diabetic veterans'. Stanford, USA. https://www.ncbi.nlm.nih.gov/pubmed/16343098
27. T. Ikeda, Y. Furukawa, S. Mashimoto, K. Takahashi, M. Yamada. 'Vitamin B12 levels in serum and cerebrospinal fluid of people with Alzheimer's disease'. Yamaguchi University, Japan. 1990 http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0447. 1990. tb01395.x/full
28. H-X. Wang, BA, Å. Wahlin, PhD, H. Basun, MD, PhD, J. Fastbom, MD, PhD, B. Winblad, MD, PhD and L. Fratiglioni, MD, PhD. 'Vitamin B12 and folate in relation to the development of Alzheimer's disease'. Stockholm, Sweden. 2001 http:// www. neurology.org/content/56/9/1188.1.short
29. Nisha G. Kemse, Anvita A. Kale, and Sadhana R. Joshi. 'A Combined Supplementation of Omega-3 Fatty Acids and Micronutrients (Folic Acid, Vitamin B12) Reduces Oxidative Stress Markers in a Rat Model of Pregnancy Induced Hypertension'. India; USA. 2014http://europepmc.org/articles/PMC4236044
30. Medha N.Munshi, AngieStone, LouisFink, VivianFonseca. 'Hyperhomocysteinemia following a methionine load in patients with non-insulin-dependent diabetes mellitus and macrovascular disease'. Arkansas, USA. 1996 https:// www. sciencedirect. com/science/article/pii/S0026049596902115
31. Anoop Misra, Naval K. Vikram, R. M. Pandey, Manjari Dwivedi, Faiz Uddin Ahmad, Kalpana Luthra, Kajal Jain, Nidhi Khanna, J. Rama Devi, Rekha Sharma and Randeep Guleria. 'Hyperhomocysteinemia, and low intakes of folic acid and vitamin B12 in urban North India'. India, 2014 https://link.springer.com/article/10.1007/s003940200010
32. Manuel R. Malinow, M.D., Paul B. Duell, M.D., David L. Hess, Ph.D., Peter H. Anderson, Ph.D., Warren D. Kruger, M.D., Beverley E. Phillipson, M.D., Robert A. Gluckman, M.D., Peter C. Block, M.D., and Barbara M. Upson, B.S. 'Reduction of Plasma Homocyst(e)ine Levels by Breakfast Cereal Fortified with Folic Acid in Patients with Coronary Heart Disease'. New England Journal Medicine, 1998 http:// www. nejm.org/doi/full/10.1056/NEJM199804093381501#t=abstract
33. Whitworth JA, Brown MA, Kelly JJ, Williamson PM. 'Mechanisms of cortisol-induced hypertension in humans'. Kogarah, Australia. 1995 https:/ /www .ncbi.nlm .nih.gov/ pubmed/7792821
34. Kelly JJ, Mangos G, Williamson PM, Whitworth JA. 'Cortisol and hypertension'. Sydney, Australia. 1998 https://www.ncbi.nlm.nih.gov/pubmed/9809193
35. Xudong Mao, MD, Xubin Xing, MD, Rong Xu, MD, Qing Gong, MD, Yue He, MD, Shuijun Li, MD, Hongfu Wang, MD, Cong Liu, MD, Xin Ding, MD, Rishu Na, MD, Zhiwen Liu, MD, and Yi Qu, MD and Yung-Hsiang Chen. 'Folic Acid and Vitamins D and B12 Correlate With Homocysteine in Chinese Patients With Type-2 Diabetes Mellitus, Hypertension, or Cardiovascular Disease'. Shanghai, China. 2016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4753885/
36. Tamai Y, Wada K, Tsuji M, Nakamura K, Sahashi Y, Watanabe K, Yamamoto K, Ando K, Nagata C. 'Dietary intake of vitamin B12 and folic acid is associated with lower blood pressure in Japanese preschool children'. Japan. 2011 https:// www. ncbi. nlm.nih. gov/pubmed/21814291
37. E P Quinlivan, J McPartlin, H McNulty, M Ward, J J Strain, D G Weir, J M Scott. 'Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease'. 359: 227–228. Lancet. 2002 http://williams.medicine.wisc.edu/b12homocys.pdf
38. Cristiana Catena, Gianluca Colussi, Francesca Nait, Frine Capobianco, Leonardo A. Sechi; Elevated Homocysteine Levels Are Associated With the Metabolic Syndrome and Cardiovascular Events in Hypertensive Patients, American Journal of Hypertension, Volume 28, Issue 7, 1 July 2015, Pages 943–950, https:// doi.org /10.1093/ajh/hpu248 Amos Gelbrad, 33 years old, Lives in Kibbutz Eilon in the Western Galilee in Israel