PREVENTATIVE HEALTH – THE MEDITERRANEAN DIET AND THE GUT MICROBIOME

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INTRODUCTION

The increase in life span has been accompanied by an increase in the occurrence of chronic, non-communicable diseases (NCDs) which affect the quality of life and independence of the ageing population. According to the World Health Organisation (WHO), NCDs are responsible for 74% of all deaths worldwide [1]. The increase in NCDs not only affects aged populations however the trend is more pronounced in ageing demographics [2].

In England, in common with many other countries, improvements in the mortality rates due to NCDs have slowed in recent years. Overall, England has an average to lower quality of outcomes when compared to other European countries [3]. The role of diet in the occurrence of NCDs in general [4] and in Alzheimer's disease in particular [5] is widely accepted.

Daily we make decisions on our diet based on perceived enjoyment and the need for nutrients. These decisions have positive or negative effects which can be attributed to the food chosen. The choice of one's diet is, together with genetic and environmental factors one of the three major influences on healthy living. Gene editing and gene therapy aside, one cannot alter the genetics with which one is born; hence the focus of this article will be on the factors we can control, namely environment and lifestyle.

It has been well documented that people living in certain parts of the world have a significantly longer lifespan than the rest of the developed world [6]. This increased lifespan has in part been ascribed to diet, which is based on a high consumption of fruit, vegetables and grains, the consumption of moderate amounts of animal products and the habit of consuming smaller meals of lesser calorific value, more frequently [7], in the context of what has come to be described as the 'Mediterranean Diet' [8]. A meta-analysis of prospective studies performed between 1966 and 2008 encompassing more than 1.5 million subjects has shown that a strict adherence to the Mediterranean diet is "associated with a significant improvement in health status" [7]. The most significant impacts reported included a reduction in mortality (9%), death from cardiovascular diseases (9%), incidence of cancer (6%) and incidence of neurodegenerative diseases such as Parkinson's and Alzheimer's (13%) [9].

Despite extensive epidemiological and other studies, the nature of the health protective factor or factors remains unclear.

Our proposition is that the multifactorial nature of those components which have been implicated is suggestive of a single target in the human body which can respond either to

several different dietary components or to something that is ubiquitous in the Mediterranean diet but at the same time influences numerous NCD outcomes. The human microbiome is a potential candidate target and particular classes of phytoprotective compounds are possible dietary components.

THE HUMAN MICROBIOME

The human microbiome is the community of microorganisms that live in a generally symbiotic relationship with the human host. Microbiomes exist in a range of organs including in the human gastrointestinal (GI) tract from the mouth all the way to the colon [10]. Other microbiomes have been found on skin [11], in the eye [12] and even perhaps in the brain [13].

The various microbiomes can affect health through the production of beneficial and harmful factors including short chain fatty acids (beneficial), B and K vitamins (beneficial) and inflammatory responses (harmful). Microbiome communities are, like human communities, in a state of benign balance. The loss of this can lead to illness and, in particular, to increases in NCDs.

The gut microbiota is made up of 1000+ species although the exact number is difficult to quantify due to individual and geographical / cultural differences between people [14]. The large number of microbial cells means that their biological effects can be significant. The gut microbiome contains up to 250-800 times the number of genes as the human genome. This leads to a high level of complexity both within the microbiome and in its relationship to the human host. The contribution that the gut microbiome makes to an individual's whole body health and wellbeing is reflected in gut-brain, gut-liver, gut-kidney and gut-heart axes [15].

BACTERIA AND BIOFILMS

The presence of pathogenic bacteria can invoke the body to initiate an immune process called phagocytosis. In phagocytosis, the body produces cells which engulf and ingest large foreign bodies such as bacteria and remove them from the cell. The process of phagocytosis is a key aspect of the defence against infection and attack by pathogens. One way that bacteria can resist phagocytosis is through the production of a protective shield called a biofilm [16]. A biofilm is an extracellular polymer matrix that protects bacteria against the body's immune system. The majority of bacteria that are implicated in disease can form biofilms.

QUORUM SENSING

Bacteria produce a range of molecules that assist them in growth and, in addition, act as signalling molecules to advise a bacterial species if it should form a biofilm community or break that community apart and migrate to other sites (this is called planktonic behaviour). One of the most common such molecules are a group of homoserine lactones called autoinducer molecules. These molecules are also implicated in the human inflammatory response to bacterial colonisation.

BITTER RECEPTOR AND PHAGOCYTOSIS

Phagocytosis is not only initiated by bacteria. While the ability to taste bitter compounds is mediated by the bitter receptor in the oral cavity, members of this class of receptor are also found in other organs including in the GI tract. In these extra-oral locations, binding of a bitter compound can induce the body to initiate phagocytosis [17]. So bitter compounds (some of which are found in the Mediterranean Diet) may help to protect against pathogens.

LACTONASE

In addition to the induction of phagocytosis, human cells can also produce an enzyme called lactonase which breaks down the quorum sensing homoserine lactone (autoinducer) and renders it biologically inert. This enzyme is found in a number of organs which are affected by inflammation including the GI tract and the brain and, if the enzyme is present then the signal to the bacteria to produce a protective biofilm does not happen.

THE MEDITERRANEAN DIET

Micobiome imbalance (dysbiosis) can allow pathogenic bacteria to multiply and to provoke a number of responses including inflammation. There is a link between lactonase production and the consumption of some fresh fruits and juices [18] so some components of the Mediterranean diet may inhibit pathogen growth by increasing the breakdown of the quorum sensing homoserine lactones, preventing biofilm formation and stimulating phagocytosis.

Besides fibre, the most abundant group of dietary phytochemicals are polyphenols. Dietary polyphenols, found in fruits, vegetables, cereals, tea and coffee and in products such as cocoa, chocolate and wine, are a heterogenous collection of compounds all containing a number of phenol rings. Dietary polyphenols may act either directly on the gut or indirectly through their metabolites. The metabolites of polyphenols may act as prebiotics and act as antimicrobials against xenobiotic organisms [19]. The prebiotic effect includes positive effects on gut epithelial integrity, maintenance of body weight, control of inflammation and insulin resistance [20]

The Mediterranean diet is known to be high in bitter phytochemicals (particularly phenolics) and if these bind to the extra-oral bitter receptor mentioned above, they could stimulate phagocytosis in the human cell and cause the removal of pathogenic bacteria [21].

CONCLUSION

Dietary phytochemicals have a significant impact on health and disease as mediated by the host-microbiota relationship which is dependent as much on an individual's genetics as well as on their environment from birth. The host-microbiota mediated effects are due to the microbial metabolites of phytochemicals acting either directly on various host-mediated metabolic pathways or via host receptor-mediated pathways.

Dietary phytochemicals can affect predisposition to obesity and diabetes, reduce risk of cardiovascular disease, affect one's inflammatory response in the gut and brain, exclude pathogens from the gut, and last, but not least, improve one's energy levels and mood. Thus, modulating one's diet to include or exclude specific phytochemicals may be as effective in maintaining one's state of health as would the use of small molecule pharmaceuticals and should be an ongoing consideration in the maintenance of personal health and wellbeing.

We have used our expertise at Biophys to examine a novel hypothesis regarding the potential chronic disease-

prevention capability of the Mediterranean diet. Our dual hypothesis (lactonase and induction of phagocytosis) is mechanistically plausible. It is possible to investigate the potential for different dietary components and mixtures to bind to the bitter receptor or to induce lactonase production. Optimisation of diets could make a significant improvement in the health of the population and reduce the burden of NCDs on the NHS.

References

1. Noncommunicable diseases. WHO Factsheet, 16 September 2023. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases.
2. Taichi Inui, A Bryan Hanley, E-Siong Tee, Jun Nishihira, Kraisid Tontisirin, Peter Van Dael, Manfred Eggersdorfer. Nutrients, 2021, 13, 2222.
3. The Burden of Disease in England compared with 22 peer countries - A report for NHS England. PHE Publications Gateway Number GW-971. January 2020.
4. Iriti M, Varoni EM, Vitalini S. Foods. 2020 Jul 16;9(7):940. doi: 10.3390/foods9070940.
5. Xu, W., Xu, Z., Guo, Y. et al. J Health Popul Nutr 43, 9 (2024). https://doi.org/10.1186/s41043-024-00503-9.
6. C. Ekmekcioglu, Critical Reviews in Food Science and Nutrition, 2020, 60(18): 3063
7. C. Davis, J. Bryan, J. Hodgson, K. Murphy, Nutrients, 2015, 7(11), 9139.
8. Dominguez LJ, Di Bella G, Veronese N, Barbagallo M. Nutrients, 2021, Jun 12;13(6):2028. doi: 10.3390/nu13062028.
9. G. Capara, Mediterranean Journal of Nutrition and Metabolism, 2018, 11, 261.
10. BMJ, 2018;361:k2179
11. Byrd, A., Belkaid, Y. & Segre, J. Nat Rev Microbiol, 16, 143–155 (2018). https://doi.org/10.1038/nrmicro.2017.157.
12. Petrillo F, Pignataro D, Lavano MA, Santella B, Folliero V, Zannella C, Astarita C, Gagliano C, Franci G, Avitabile T, Galdiero M. Microorganisms, 2020 Jul 13;8(7):1033. doi: 10.3390/microorganisms8071033.
13. Link CD. Neurosci Insights, 2021 May 27;16:26331055211018709. doi: 10.1177/26331055211018709.
14. J. Yang, J.Pu, S. Lu, et al, Frontiers in Microbiology, 2020, 11, 2029.
15. K. Oliphant, E. Allen-Vercoe, Microbiome, 2019, 7, 91.
16. Zhao A, Sun J, Liu Y. Front Cell Infect Microbiol, 2023 Apr 6;13:1137947. doi: 10.3389/fcimb.2023.1137947.
17. Gopallawa I, Freund JR, Lee RJ. Cell Mol Life Sci, 2021 Jan;78(1):271-286. doi: 10.1007/s00018-020-03494-y. Epub 2020 Mar 14.
18. Aviram M, and Rosenblat M. (2012). Evid Based Complement Alternat Med, 2012, 382763.
19. X. Tsounis, A. Rodriguez-Mateos, J. Vulevic, et al, American Journal of Clinical Nutrition, 2011, 93, 62.
20. M. Jayachandran, J. Xiao, B. Xu, International Journal of Molecular Science, 2017, 18, 1934.
21. Cavallo C, Cicia G, Del Giudice T, Sacchi R, Vecchio R. Nutrients, 2019 May 24;11(5):1164. doi: 10.3390/nu11051164.