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Review Article

A Nutritional Link for COVID-19?

T Colin Campbell*

Jacob Gould Schurman Professor of Nutritional Biochemistry, Cornell University, United States

***Corresponding Author:** T Colin Campbell, Jacob Gould Schurman Professor of Nutritional Biochemistry, Cornell University, United States.

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Abstract

Nutrition is seldom considered to be a factor in the occurrence of viral diseases, including COVID-19. The findings reported here question this impression.

I draw on data from a comprehensive survey of diet, lifestyle and disease mortality among a survey of 8990 adults residing in rural China in 1989. Among a large number of variables, this paper focuses on the association of multiple nutrition factors with hepatitis B virus (HBV) and its causation of liver cancer.

Animal food consumption, very low by Western standards, associates with increased viral infectivity and outcome (liver cancer mortality) but with less immunity. Plant food consumption shows the opposite, less antigen (infectivity) and more antibody (immunity). In a companion study, animal protein markedly promoted liver cancer development in HBV-transfected transgenic mice. All correlations and experimental results were statistically significant, almost all highly significant ($p < 0.001$).

These findings support the hypothesis that this same nutrition, involving the immune system among other systems, applies to COVID-19 as well.

Keywords: *Infectivity; Immunity; COVID-19; Hepatitis B Virus (HBV); Liver Cancer*

Introduction

Although an exceptional amount of information has been published on the COVID-19 pandemic since its arrival in late 2019 and early 2020, it is disappointing that so little attention, if any, has been given to a role for nutrition either in the etiology or in the clinical management of this disease. This is concerning because, for much too long, very little experimental research has been conducted on an effect of 'nutrition' on viral diseases as a class. Such neglect negates, in principle, what individuals might do for themselves, such as managing these diseases by the foods they choose to eat.

A 1996 symposium [1,2], which was sponsored by the professional nutrition research society, the American Society for Nutrition[a] and which was entitled "Nutrition and newly emerging viral diseases: an overview", shows how negligent we have been. The symposium presentations, although informative, mostly relied on what I consider to be an unfortunate misunderstanding of nutrition [3,4]. One

[a]I have been a full member in this society for more than fifty years.

perspective has long assumed that malnutrition refers to specific nutrient and calorie deficiencies more commonly observed in impoverished, economically poor societies whereas now, malnutrition should also include overconsumption of unhealthy foods typically eaten in economically affluent societies. A second perspective, which is full of misunderstanding and confusion, assumes that nutrition represents a simple summation of the independent effects of single nutrients in food acting on targeted mechanisms to produce specific outcomes. In contrast, I describe nutrition as a comprehensive, wholist effect of clusters of nutrients having common purpose, each nutrient cluster composed of smaller clusters of highly integrated physiological and biochemical mechanisms to control a broad spectrum of related disease and health outcomes [5]. Assumptions of independent nutrient effects have important public implications, such as increasing the opportunity to establish national dietary guidelines around presumed single nutrient effects as if they had broader dietary scope. Opportunities for such mischief are boundless. The U.S. Department of Agriculture[b] updates every five years [6] the nationally influential dietary guidelines are derived from recommended intakes of individual nutrients established by the Institute of Medicine of the U.S. National Academy of Sciences [7]. These misguided perspectives, which have a long history [8] must be addressed if effects of nutrition on viral and related disease and health events, are to be understood. A renaissance in nutrition is needed [5].

Types and methods

Here, I will consider the nutrition-viral disease association by using data collected in an unusually comprehensive survey of diet, lifestyle and disease mortality characteristics in 69 counties (duplicate villages in each county) in mainland China in 1989 [9]. This was a repeat of an earlier 1983 [10] survey (362 characteristics/variables) for 65 of these same 69 counties and households[c] along with 16 areas in Taiwan and 4 new counties in mainland China. These 1989 data used for this publication are limited to the counties in mainland China, wherein 639 characteristics/variables were recorded [9]. These included 119 disease mortality rates, 200 laboratory analytes (plasma, red blood cells, urine), 148 dietary exposures (three-day household weighing of food per reference man) and 247 questionnaires (dietary, lifestyle, anthropometric, social and economic factors)[d].

Univariate correlations were determined for each of the 639 variables paired with every other variable. Data utility and reliability were assessed by comparing homogeneity of data within duplicate villages in the same county with the heterogeneity of data across all counties. Data characteristics were displayed by histograms of data distribution, scatter plot comparisons of within-county, between-village and between-gender variables, by distribution of variables by quartiles across mainland China, and by comparisons of 1983 and 1989 data. Two-page compilations of 'raw' data for each variable, for each village, for each gender, within each county (with summaries of means, medians and t-tested correlations) were published for the 1983 monograph in mainland China [10] whereas only the statistically significant ($P < 0.05, < 0.01, < 0.001$) correlations for each variable with every other variable were published for the 1989 survey (over 10,000 statistically significant correlations). This provided an opportunity to investigate cause-effect hypotheses not only by considering univariate correlations independently, but more importantly by considering statistically consistent and biologically plausible clusters of correlations. Initial reports on the 1983 database were published in 1994 [11-16].

Nutritional setting

As expected, animal protein directly correlates with intakes of meat ($r = 0.80$), poultry ($r = 0.37$), fish $r = 0.84$) and cholesterol ($r = 0.91$), and with serum levels of cholesterol ($r = 0.69$), while plant protein intake correlates with intakes of plant-specific thiamine ($r =$

[b]In partnership with the Department of Health and Human Services.

[c]To the extent possible, with replacements to compensate for death or migration.

[d]The total number of variables is 639, but some of the same variables were recorded in more than one way, thus giving 714 entries.

0.63) and dietary fiber (0.66), but inversely with serum levels of cholesterol (r = -0.44) (Table 1). Each of these eight correlations is highly statistically significant (p < 0.001), demonstrating for serum levels of cholesterol opposing animal and plant-based food associations producing the same outcome. This association of animal protein with serum levels of cholesterol is especially noteworthy because protein intake was very low (survey mean of 7.4 g/day and range of county means 0 - 29 g/day) when compared with the U.S. (approximately 60 - 65 g/day) [17]. The same correlation existed six years before, in 1983, when animal protein consumption was even lower (mean of 5.3 g/day and range of 0 - 24 g/day[e]). Making these findings even more remarkable and noteworthy was the simultaneously low range, by Western levels, of serum cholesterol (1989 county mean of 147 and range of 122 - 185 mg/dL and a 1983 county mean of 127 and range of serum cholesterol of 94 - 162 mg/dL).

Variable A	Variable B	R (%)	P <
Animal protein, g/day (reference man)	Red meat, g/day	+80	0.001
	Poultry, g/day	+37	0.01
	Fish, g/day	+84	0.001
	Saturated fat, g/day	+66	0.001
	Dietary cholesterol, mg/day	+91	0.001
	Serum total cholesterol, mg/dL	+69	0.001
	Serum LDL cholesterol, mg/dL	+52	0.001
	Liver cancer mortality	+42	0.001
Plant protein, g/day (reference man)	Serum testosterone, ng/mL[1]	-58	0.001
	Urinary urea/creatinine, mg/mg[2]	+58	0.001
	Serum total cholesterol, mg/dL	-44	0.001
	Dietary thiamine, mg/day	+72	0.001
	Dietary fiber, g/day	+66	0.001
	Animal protein, g/day	-63	0.001
	Liver cancer mortality	-44	0.001

Table 1: *Nutritional factor correlations.*

In 1983, it was initially thought that such low serum levels of cholesterol, by Western standards (comparable range of 155 - 274 mg/dL, mean of 212 mg/dL), might be incorrect, but additional analyses (Cornell, Oxford, Beijing) confirmed these values. Statistically significant increases in serum cholesterol starting from near zero animal protein intake has not been previously reported, to my knowledge. Further, the correlation of serum cholesterol vs. dietary animal protein appears to extend a continuum of the same correlation observed at much higher levels of animal protein in Western societies [18,19]. It should also be noted that serum cholesterol, for an entire society, can change relatively quickly. Within six years, from 1983 to 1989, population-based serum cholesterol increased 16%, in parallel with a 25% increase in dietary fat (from 14.6 to 18.3%) and a 40% increase in animal protein consumption [9]. This rapid dietary transition followed Chinese premier Deng Xiaoping's economic reform in the late 1970s [20].

[1]Mostly related to animal food (r = +39%, p < 0.01) and plant food (r = -41%, p < 0.001).

[2]Highly associated with plant food intake (dietary fiber, r = +58%, plant protein r = +58%, both p < 0.001).

[e]Excluding one northern county in the ethnic Muslim area (134 g/day) where larger amounts of dairy and meat were being consumed during a feast at the time of the survey. Median intake for all counties was 2.5 g/day.

An earlier analysis [16] of the 1983 survey in mainland China showed that disease mortality rates tended to concentrate geographically into two groups. One group represented quasi-urbanized counties, whose characteristics trend in the direction of economically affluent Western countries (cardiovascular, cancer, diabetes, etc.) while the other geographic group represented rural counties whose characteristics are similar to economically disadvantaged countries (communicable diseases). Most of the counties of that 1983 survey in mainland China, and used again in 1989, were intentionally selected from mostly rural areas where residency might be stable and food consumption is be locally produced. Indeed, 94% of the survey residents were born in the counties where they were surveyed [10]. Hypothesizing that each disease group shares common causality-at least to some extent, it was found that increasing serum cholesterol was highly significantly ($p < 0.001$) correlated with a higher rate of Western diseases. This same correlation exists for Western diseases versus higher serum cholesterol in the U.S., but at a much higher range of serum cholesterol.

Nutrition and hepatitis b virus

Mortality for virus-caused liver cancer correlates (Table 1) positively with animal protein ($r = +42\%$, $p < 0.001$) but inversely with plant protein intake ($r = -44\%$, $p < 0.001$). Corresponding to this finding, plant-based food consumption correlates with more antibody ($r = +29\%$, $p < 0.05$) and less antigen, based on several biomarkers of plant food intake ($p < 0.01$ to < 0.001) (Table 2). Animal food intake, even though very low by Western standards, still correlates with less antibody ($r = -31\%$, $p < 0.05$).

Immune Biomarker	Variable	R (%)	P <
HBV antibody, % positive, individual samples	Dietary cholesterol, mg/day	-27	0.05
	Animal food, g/day	-31	0.05
	Plant food, %	+29	0.05
	Light vegetables, g/day/fresh weight[1]	+39	0.001
HBV antigen, % positive, individual samples	Dietary fiber, g/day	-37	0.01
	Dietary thiamine, mg/day	-46	0.001
	Dietary plant protein, % kcal	-44	0.001
	Dietary polyunsaturated fat, %[2]	-34	0.01
	Monounsaturated fat, % of fat intake	+40	0.001
	Dietary rice, g/day[3]	+40	0.01
	Urinary urea/creatinine, mg/mg	-46	0.001
	Serum testosterone, ng/dL	+32	0.01
	Liver cancer mortality	+38	0.01

Table 2: *Virus biomarker correlations.*

[1]Mostly high fiber grains, green vegetable intake very low in China, 154 g/day (wet weight) or about 15 g/day dry weight (one-half ounce)-too low to be meaningful.

[2]Highly correlated with plant protein ($r = +61\%$, $p < 0.001$), inversely with animal protein ($r = -46\%$, $p < 0.001$).

[3]Almost all rice in China is refined, ($r = -60\%$ with fiber; -76% plant protein, $p<0.001$, $r = +26\%$, $p < 0.05$ with animal protein and $r = +35\%$, $p < 0.01$ with meat).

More than 10,000 statistically significant correlations (from $p < 0.05$ to $p < 0.001$) are available in this very large database, thus raising a risk of confirmation bias when selecting and interpreting univariate correlations out of context. This concern, of course, is founded on the assumption that single factors are causes and cures of complex diseases. This assumption, although widely assumed for many decades-as in the pharmaceutical and nutrient supplement industries, it is not applicable for nutrition which involves many nutrients working together. Therefore, to minimize this risk of bias, however applicable it may be, I group biologically plausible, statistically significant correlations tracking together as a cluster of correlations which can better defend the hypothesis. Any outliers, fewer by definition, then need recognition and explanation, if possible [5].

All of the statistically significant correlations presented here (Table 1 and 2) support the hypothesis that plant-based nutrition favors virus immunity, thus decreasing its principal outcome, primary liver cancer mortality. Yet, there was one unexpected outlier, urinary excretion of urea nitrogen (UUN), generally assumed to indicate elevated protein intake.

UUN is inversely correlated with more antigen ($p < 0.001$), suggesting that high protein intake (presumably from animal sources?) represses HBV antigen prevalence. In contrast, UUN also associates with indicators of greater plant food consumption, including plant protein intake ($r = +58\%$, $p < 0.001$), polyunsaturated fat intake ($r = +55\%$, $p < 0.001$) and lower meat intake, ($r = -42\%$, $p < 0.001$). If UUN is therefore accepted as a marker of plant food consumption, it adds further evidence for the hypothesis that plant food consumption favors virus immunity. A second puzzling correlation suggests that plant-derived vitamin C intake correlates with more antigen, albeit weakly, when it was expected to associate with less antigen. I have no explanation for this apparent anomaly, leaving the possibility of a random error or an analytical problem. Setting aside this puzzling correlation, the overwhelming evidence supports the hypothesis that plant-based foods repress while animal-based foods favor virus-caused liver cancer mortality ($p < 0.001$), likely involving the immune system. This is evidenced by a two-by-two set of highly significant correlations of plant and animal food intakes and antigen and antibody responses.

Laboratory animal studies as additional plausibility

Additional evidence for this hypothesis came from companion lab experiments which investigated the effect of dietary protein fed to mice transfected with a DNA fragment of the hepatitis B virus gene, which acts as a complete carcinogen to produce liver cancer [21-23]. Virtually all HBV-transfected mice normally develop liver cancer but, in our studies, this was almost completely modified by the feeding of animal protein (casein) in excess of its requirements (about 6 percent of diet calories). Higher dietary protein (14 and 22 percent) fed for 3 - 6 months showed dramatic increases in liver cancer growth, as shown by liver content of HBV surface antigen (HBsAg), by its RNA transcripts and by serum gamma glutamyl transpeptidase (GGT), a biomarker of cancer development. Also, 14 and 22 percent dietary protein increases, in a dose dependent manner, hepatic insulin-like growth factor (IGF-2) [24,25] and tumor development at 15 months [26]. Extrahepatic serum levels of HBsAg increased by 1.6-, 2.1- and 5.1-fold in animals fed 6, 14 and 22 percent animal protein (casein) diets over non-transgenic control animals. This huge promotional effect of animal protein on experimental cancer development is similar to other experiments in our laboratory [27-29], showing that animal but not plant protein [30] markedly promotes pre-neoplastic and neoplastic (tumor) stages of liver cancer in rats initiated by the potent carcinogen, aflatoxin, a fungal metabolite. The tumor enhancing effect by animal-based protein acts through countless mechanisms operating in symphony, one of which was a depressed level of the immune factor, natural killer cells [12].

Consistency of evidence

This observation that animal-based protein both correlates with liver cancer in human studies ($p < 0.001$) and promotes liver cancer in two types of laboratory animal studies is unusually convincing. First, the human subject evidence in rural China exists for very low animal protein intake, which was only about 10% of U.S. intake. Yet this was enough to demonstrate highly significant ($p < 0.001$) correlations both for liver cancer mortality and for increasing serum cholesterol, which correlated, in turn, with Western degenerative diseases as a

group [16]. Second, a correlation of increasing disease with increasing animal protein-based foods in human studies will undoubtedly include a contribution by decreasing intakes of plant protein-based foods, thus enhancing an plant food effect otherwise ascribed to animal protein. Third, when nutrition represents a large number of mutually supportive, biologically plausible causal agents, mechanisms and disease outcomes [5], the totality of the evidence is biologically plausible, an essential criterion of Hill's recommendations for epidemiological studies [31]. Fourth, this diet and disease association with a viral disease is virtually the same-at least in direction-as the association of this same diet with degenerative diseases. Fifth, whole plant food prevents and even treats (reverses) a broad range of chronic degenerative diseases, promotes superior physical performance [32,33] and extends morbidity-free years of life [34] and it does so by a multiplicity of highly integrated physiological and metabolic systems that I consider to be wholistic [5,35] a core feature of Nature herself.

Human evidence on viral initiated liver disease

The evidence cited here is consistent with a 2009 study [36] reported on the dietary causes of liver disease (liver cirrhosis, liver cancer) for 9221 U.S. citizens aged 25 - 74 years, without evidence of cirrhosis from the start of the study and during the first 5 years and subsequently followed for disease occurrence for a mean of 13.3 years. These persons were enrolled in the first U.S. National Health and Examination Survey (NHANES) in 1971 - 1975, a cross-sectional dietary survey that now is routinely repeated every two years. For this study, subsequent disease mortality was obtained in additional follow-up surveys until 1992.

The initially stated purpose for this investigation by these investigators was to assess the contribution of fat and carbohydrate consumption on the occurrence of hepatic diseases often associated with fatty liver and primarily caused by a hepatitis virus[f]. In this analysis, total fat was not significantly associated with death rates from cirrhosis or liver cancer. Although not originally hypothesized, the researchers surprisingly found that persons consuming more protein ($P < 0.001$) and cholesterol ($p = 0.007$) but less carbohydrate ($p = 0.003$) were at higher risk of disease. These diet associations, along with a non-significant increase in polyunsaturated fat (mostly plant derived) associated with less disease, reflect consumption of more plant-based and less animal-based foods. The authors suggested that these associations may have been even larger because of certain methodological issues. This evidence becomes more convincing when most these cohort subjects undoubtedly consumed a generous amount of animal-based protein which likely compromised the experimental sensitivity of detecting such a statistically significant association.

This evidence in its totality includes a broad and varied range of experimental settings which collectively show highly statistically significant effects of nutrition. The finding of the association of nutrition with viral disease may be the most noteworthy finding and with- in this nutrition effect, it is made even more significant by the low range of animal protein consumption. In rural China, the regression of disease occurrence on animal protein consumption occurs over a very low range of animal protein consumption [16] whereas in the U.S., the same regression occurs for a range bracketing a substantially higher range of protein intakeg. This disease enhancing association with animal protein consumption undoubtedly combines with decreasing plant protein consumption, as opposed to the independent effects of animal protein or any other nutrient, however significant these effects may be.

[f]There are 5 types of hepatitis virus, A, B, C, D, and E with varying symptoms and degrees of seriousness; HBV is the most serious, with annual world deaths well over 700,000 per year.

[g]The researchers of the U.S. study [36] were not able to disassociate animal and plant proteins content but it is known from other studies that approximately 70-75% of the total protein was animal-based [37,38].

Implications for COVID-19

In view of the breadth, biological plausibility, and statistical consistency of this nutrition centered evidence, both for this viral disease in rural China and for the well documented effect on many degenerative diseases, I hypothesize that the nutrition provided by a diet of whole plant-based foods will minimize if not prevent symptom severity of viral diseases like COVID-19 caused by the SARS-CoV-2 virus. If nutrition is understood as a wholistic concept which expresses effects akin to Nature, she would not prevent and treat one group of diseases in one way while treating another group in an opposite way. For these reasons and the relative weight of this evidence, I am confident that this hypothesis on COVID-19 deserves serious attention. Add to this observation that dietary intervention of whole, plant-based foods acts quickly. For example, heart disease patients, upon dietary intervention, experience a 20 - 30% decrease in serum cholesterol within 2 - 3 days [39-41]. Type 2 diabetics, who medicate to control blood sugar, are advised to closely monitor their response when starting this diet because of its potent ability to repress blood sugar that could cause hypoglycemic shock if the medication were combined with the diet [42-44]. In a case study of a 69-year old male diagnosed with stage 3 chronic kidney disease, diabetes and hypertension and using nine pharmaceuticals, intervention with this diet, insulin medication decreased from 201 to 70 units in four days [45] and all but two of the pharmaceuticals were suspended.

This hypothesis may be even more appropriate to consider when comparing it with the social and public health advisories now ad- vocated for managing covid-19, as well as viral diseases of uncertain severity yet to appear. Whereas it is important to note that, in this calculus although, this hypothesis is not yet directly proven, it also is important to recall that its worthiness is relative to the present confidence in the disease control strategies now being advocated. The breadth of this nutritional effect to prevent and reverse (treat), in several cases [41,42,45,46], a variety of degen- erative diseases, while simultaneously supporting physical fitness [32,33] is testimony to a fundamental, broad-based and very natural effect of food on human health. Provided that information on the pros and cons of the hypothesis are made fully transparent, choosing a nutrition protocol to control this and related diseases is the responsibility of individual users. They simply have the right to know the most reliable information for them to be able to make their own decisions.

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