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Nutritional deuterium depletion and health: a scoping review

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Abstract

Introduction Large variations in fatty and amino acid natural $^{2}H/^{1}H$ ratios in reference with solvent water point to the active involvement of compartmental, inter- and intramolecular deuterium disequilibrium in adaptive biology. Yet, the human deutenome is an untapped area of energy metabolism and health in humans.

Objectives The purpose of this scoping review is to examine health effects through deuterium homeostasis using deuterium-depleted water and/or a deuterium-depleted diet. We also aim to reveal health effects of nutritional, metabolic and exercise ketosis, i.e. complete mitochondrial fatty acid oxidation with the production of deuterium depleted (deupleted) metabolic water.

Methods A protocol process approach was used to retrieve current research in deuterium depletion according to the preferred reporting items protocol for systematic reviews and meta-analyses, extension for scoping reviews with checklist (PRISMA-ScR).

Results Fifteen research articles were used. All retrieved articles were heterogenous in nature and additional themes did not evolve. Deuterium depletion was found to have beneficial health effects in the following conditions: cancer prevention, cancer treatment, depression, diabetes, long-term memory, anti-aging, and sports performance. Deutenomics is actively pursued in drug research and there are biomarker roles attributed to large natural variations with adaptive significance in biology.

Conclusion Even with limited data, consistent deuterium depletion can be seen across all conditions reviewed. More randomized control trials are recommended to confirm cause and effect for translationally and clinically informed integrative nutrition-based medical interventions.

Keywords Deutenomics · Mitochondria · Health · Ketogenic diet · Cancer · Nutrition · Diabetes · Metabolic water · Human deutenome project

1 Introduction

Nutrition profoundly affects our health. There is so much nutrition information everywhere that it is hard to find reliable guiding principles based on paramount components rooted in medical biochemistry, mitochondrial substrate oxidation foundations, and cellular energy production. Mainstream puts a spotlight on the many facets of a diet, but there's another spoke on the wheel that has potentially slipped under the radar that may have an impact on health—heavy hydrogen, i.e. deuterium. Deuterium content in water and food consumption is not a popular or even known topic. For these reasons, a scoping review was conducted to provide existing knowledge in the field and map the research done in this area. For this review, the following research question was formulated: "Does nutritional deuterium depletion have an impact on health?".

Hydrogen (^{1}H) is the first atom in the periodic table that has a naturally occurring stable isotope, called deuterium (^{2}H, D) with double mass and size of its atomic nucleus. Hydrogen has one proton in its atomic nucleus, whereas deuterium has one proton and one neutron, giving it a mass number of 2 (Urey et al., 1932) that result in significant differences in its behavior in hydrogen bonding biological networks (Olgun, 2007). This is because regarding stable

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isotopes of the same element, hydrogen and deuterium have the largest (~ 100%) mass difference, which causes magnitude differences in physical and chemical properties. In nature, the ratio of deuterium to hydrogen (D/H) ratio is about 1:6600; the natural concentration of deuterium and in the human body is about 150 ppm (parts per million) or 12 to 14 mmol/l (Somlyai et al., 1993, 2023b). Published in 1993 was the first paper illuminating that reduced deuterium-concentration has an impact on living organisms. There are many proposed mechanisms for this.

The underlying mechanisms is referred to as deuteration, i.e. the process of introducing deuterium into a molecule or chemical compound in place of a hydrogen. Such substitutions in ATPase, including both ATP synthase and ATP hydrolase, exert devastating biological consequences (Olgun, 2007). ATP synthase is an inner mitochondrial enzyme complex to tunnel protons from the intermembrane compartment to the matrix (innermost confinement) of mitochondria. It uses protonation (addition of a proton) to produce a wheel-like rotation to make ATP, which is the energy currency in living systems. Partial deuteration of the H^+ system led to unequal protons, which destroys proton tunneling (Drechsel-Grau & Marx, 2014). Increasing D/H ratio in the intracellular space has been shown to be a determinant in cell growth (Somlyai et al., 1993). Deuterium is precisely regulated in biology via either depletion (deupletion) during mitochondrial citrate synthesis to protect rotary (moving) proteins such as ATPase nanomotors (Olgun, 2007) or accumulation, on the other hand, in structural proteins such as bone collagen with adaptive impact (Gharibi et al., 2022).

2 Scientific evidence of Deutenomics in peer reviewed medical literature

Deutenomics is the translational science of biological deuterium fractionation and discrimination in Nature in order to address clinical and epidemiological trends in health via nutrition related biochemical processes in various sub molecular enzyme reaction compartments. As an example, natural fatty acid availability for peroxisomal, then complete mitochondrial oxidation, is considered an effective deupleting mechanism across various cancers with translational and clinical significance (Boros et al., 2017, 2024a, 2024b; Somlyai et al., 2023a). For example, metabolites from a study related to improved lung cancer patient survival are long chain fatty alcohols, which result from oxidative processing in peroxisomes or from dietary sources (Hao et al., 2016). These are ketogenic substrates that are lower in deuterium content (105–130 ppm). When the mitochondria process ketogenic substrates, it leads to the making of metabolic/matrix water via beta-oxidation with relatively low deuterium (Somlyai et al., 2023b). Oppositely, pentose phosphate cycle derived NADPH will have raised deuterium content, and raised markers from these substrates are correlated with reduced cancer survival (Boros et al., 1998).

Defective mitochondria in renal cell carcinoma can dictate tumor transformation by deuterium oncoisotope accumulation (Pandey et al., 2020). Thus, extracellular deupletion acts as a metabolic therapeutic adjuvant and it can be introduced by diet and drinks (Boros et al., 2016, 2017). Recent studies indicate diet as the main source of increased fatty acid pool in plasma; thus, production of ketones using these deuterium-depleted fatty acids might illustrate the benefit of ketogenic diets in a breast cancer epidemiological study (Santaliz-Casiano et al., 2023). An additional study reiterates the importance of inadequate mitochondrial deuterium depletion, resulting in oncogenic transformation in colon cells via metabolic profiling (Arima et al., 2020). Regarding the scientific information and evidence available on Deutenomics in peer reviewed medical literature, there is a clear justification for this review.

2.1 Deuterium depletion in nutrients

How much deuterium will be in human cells depends on a number of factors. Firstly, the deuterium concentration of fluid intake. Secondly, deuterium concentration of nutrient molecules because after oxidation of carbohydrates, proteins, and fats by the mitochondria, metabolic water is produced with decreasing deuterium content, in the same order. Oxidation of glucose produces metabolic water with higher deuterium levels and carbohydrate-rich diets will lead to the production of metabolic water with a deuterium concentration around 155.75 ppm. When the mitochondria oxidize fats/lipids, it produces metabolic water with as low as 118 ppm deuterium concentration (Somlyai et al., 2023b). It is important to remember that 100 g of fat produces 110 g of metabolic water, while 100 g of carbohydrates yields only 55 g of it (Mellanby, 1942).

Deuterium depletion can be also acquired in living organisms through the consumption of deuterium-depleted water (DDW) (Gyöngyi et al., 2013). In regular bottled water, deuterium concentration is usually between 135 and 158 ppm. Consuming 1.5–2 l of DDW with 105 ppm deuterium content day by day resulted in a serum deuterium level decrease of about 1 ppm per day (Somlyai et al., 2023a, 2023b). The continued use of DDW with the same deuterium level led to an equilibrium.

Deuterium depletion can also be attained through eating a lower deuterium content diet (Lech et al., 2021). Grass-fed (ketogenic) animals showed a lower deuterium content (< 130 ppm) while artificially mixed grain-fed (metabolically glycogenic) animals had higher deuterium content (> 140 ppm). In dairy cows, the interference of the deuterium-depletion process leads to the burning of high deuterium

nutritional products into metabolic water upon oxidation in the human body; this could contribute to the same metabolic conditions and diseases for humans that it had for cows. Grain feeding usually includes the use of glyphosate herbicide in genetically modified crops; this limits oxygen delivery to mitochondria for efficient deuterium-depleted metabolic water production. Glyphosate contaminated grain feeding of dairy cows presents odd-chain fatty acids with branched chain amino acids into metabolism by way of the tricarboxylic acid (TCA) cycle and disturbs mitochondrial proton tunneling because of the high deuterium metabolic water production with health compromising effects in the human consumer. This study's results suggest that high deuterium content of processed dairy products that come from grain-fed cattle, as a significant contributing factor to degenerative and metabolic disease conditions (like obesity, diabetes, cancer, and Alzheimer's) (Lech et al., 2021).

The purpose of this scoping review is to examine deuterium depletion through deuterium-depleted water and a deuterium-depleted diet (natural ketosis) and possible health effects.

2.2 Methods of examining deuterium, its regulation and health

A scoping review was the most appropriate method due to the rationale that deutenomics is an emerging topic in basic and applied clinical sciences. This scoping review followed the PRISMA-ScR (Peters et al., 2020) for scoping review checklist (Supplement 1). Data extraction table was created and entered by one researcher (Supplement 2) for subsequent review and validation. The inclusion criteria included original research identifying nutritional deuterium depletion and health. Exclusion criteria included secondary and tertiary sources. All study designs included human and animal data. The inclusion dates were 2008 until the present time 2024 and written in English. Search engines used were: PubMed, Wiley, Elsevier, and ResearchGate. Evidence searching terms included "deuterium, deuterium depletion, deuterium depleted water, deuterium content, deuterium-depleted water, effects of deuterium depletion, deuterium depleting nutritional ketosis, deuterium depleted water effects, deuterium level, deuterium concentration". Articles that were highly relevant to the topic and matched any one of the above terms were selected. The standard PRISMA Scoping Review Checklist was used as described in Supplement 1.

3 Results

3.1 Study disposition

Seventeen studies were identified addressing deuterium depletion and health research across various study designs published between 2008 and 2024. Two papers were excluded due to lack of full English text or translation. There were no duplicate articles. As a result, 15 articles are included in this review. Data extraction is provided in Supplement 2.

3.2 Themes

All retrieved articles were heterogenous in nature. Themes did not evolve. Below describes data in the health categories.

3.3 Cancer

Studies that have confirmed the role of deuterium in prevention of cancer development

In mice that were exposed to chemical carcinogen, the survival data after 1-year showed that drinking deuterium-depleted water (30 ppm) prevented tumor development. As shown 97.3% of genes were upregulated when the deuterium concentration in media was higher-than-normal (300 ppm) (Kovács et al., 2022).

The same study showed that blocking the increase of intracellular deuterium concentration prevents the expression of cancer-related genes, tumor development, and tumor recurrence in cancer patients. In 204 cancer patients with remission, who drank deuterium depleted water, 77.9% did not relapse, while 8 out of 11 deaths happened after stopping drinking deuterium depleted water. The proposed mechanism is preventing the D/H ratios (through drinking deuterium-depleted water) to reach the threshold necessary for cell division; suggesting that this could be a solution to reducing the relapse rate of cancer in patients and/or decreasing the cancer incidence in healthy people (Kovács et al., 2022).

3.4 Anticancer effect of deuterium depletion

Somlyai et al. showed that when laying hens' normal drinking water was replaced with deuterium-depleted water (25 ppm), the deuterium level of the albumin in their egg decreased from 160 to 110 ppm in 42 days. Similarly, they observed a decrease in the deuterium content of the yolk; proving the deupleting influence it has on the body. In two in vivo mouse models: one model 4T1 cell line with high metastatic capacity to lung showed deuterium depleted water and/or deuterium depleted yolk led to smaller tumor volume. In the group treated with deuterium-depleted yolk there was a significant difference in smaller tumor weight ($p = 0.0354$). The decrease in metastasis suggests that deuterium depletion may inhibit migration. Mice transplanted with an MCF-7 breast cancer cell line showed that the anticancer effect of deuterium depleted water was enhanced by yolk containing deuterium-depleted nutrients (Somlyai et al., 2023b).

Cong et al. determined that deuterium depleted water inhibits lung tumor growth in vivo as well as inhibited the proliferation of A549 cell lines with an accompanying increase in apoptosis (Cong et al., 2010). Tumor weight was decreased, alike. In the deuterium-depleted water group, tumor inhabitation rate was 30%. In A549 cells treated with deuterium-depleted water (50 ppm), the increase in apoptosis formation was significant ($p < 0.05$) (Cong et al., 2010).

Kovács et al. in a human, double-blind, randomized, 4-month long, phase II, placebo controlled, clinical trial showed that deuterium depletion delays the progression of prostate cancer. In the prospective trial, in the treated group (deuterium-depleted water at 85 ppm) versus placebo group (normal water at 150 ppm), they achieved the following: partial response ($p = 0.046$), net decrease in prostate volume was three times higher ($p = 0.0019$), urination complaints stopped at a higher rate ($p = 0.0041$), and 1-year survival rate was higher ($p = 0.034$). (Kovács et al., 2011).

Krempels et al. in a human, case-controlled, retrospective evaluation showed deuterium depletion in addition to conventional treatments, improves mean survival in lung cancer. In the four patients consuming deuterium-depleted water survival time was 26.6, 54.6, 21.9, and 33.4 months, respectively, which is unique in the records of brain metastases from lung tumors (Krempels et al., 2008).

Somlyai et al. in a human preliminary study showed that deuterium depletion in combination with conventional therapy improved median survival time of patients with glioblastoma multiforme (GB). The patients who drank deuterium-depleted water (85, 65, 45, and 25 ppm) had a longer median survival time by 30 months, compared to the historical control (12.1–14.6 months) (Somlyai et al., 2023a, 2023b).

Krempels et al. in a human retrospective study showed that deuterium depleted water in combination with or as an extension of conventional therapies, prolonged median survival time in certain subgroups of breast cancer patients. Deuterium-depleted water (65–105 ppm) versus normal tap water (150 ppm) prolonged median survival time in comparison with published data (Krempels et al., 2013).

Gyöngyi et al. showed in a clinical study involving 129 patients with small cell and non-small cell lung cancers who drank deuterium-depleted drinking water in addition to conventional chemotherapy and radiotherapy that the median survival time was 25.9 months in males and 74.1 month in female patient, which was statically significant ($p < 0.05$). For women with tumors overexpressing cancer-related genes, those who drank deuterium-depleted water had a median survival time that was 2–4 times longer than what is typically seen in lung cancer patients. Gyöngyi et al. also did a study of gene expression analysis in mouse lung indicating that deuterium-depleted water attenuates 7,12-dimethylbenz(a) anthracene (DMBA) induced expression of Bcl2, Kras, and Myc in females (Gyöngyi et al., 2013).

Boros et al. showed triple survival time in pancreatic adenocarcinoma patients who were treated with conventional chemotherapy and deuterium-depleted water (at 85 ppm DDW then gradually decreased to preparations with 65 ppm and 45 ppm deuterium content for each 1 to 3 months treatment period). The mean survival time for patients consuming DDW treatment ($n = 56$) was 19.6 months in comparison with the 6.36 months mean survival achieved with chemotherapy alone ($n = 30$). There was a strong, statistically significant Pearson correlation ($r = 0.504$, $p < 0.001$) between survival time and length and frequency of DDW treatment (Boros et al., 2021).

3.5 Deupletion in depression

Strekalova et al. showed in mice that substitution of normal drinking water with deuterium-depleted water (91 ppm) counteracted the depressive-like state (Strekalova et al., 2015).

This epidemiological study showed a significant positive correlation between geographical distribution of the deuterium content of natural tap water in the US population and rates of depression. There was a significant correlation ($p = 0.0016$) between deuterium content of tap water and rates of depression. From the data it was estimated that the prevalence of depression is increased 1.8% for every 10-ppm increased deuterium in tap water ($p = 0.0016$). The authors concluded that deuterium content of drinking/cooking water affects chronic mental disease susceptibility (Strekalova et al., 2015).

3.6 Diabetes (metabolic regulation of deuterium)

Molnár et al. confirmed that deuterium depletion, in a dose-dependent manner, enhanced the effect of insulin on Glucose Transporter type 4 (GLUT4) translocation. In diabetic rats, it potentiated glucose uptake, which led to lower serum glucose, fructose amine, and HbA1c concentrations. An animal study of rats, showed that the optimal deuterium concentration of blood for reducing blood sugar levels was 125 and 140 ppm (Molnár et al., 2021).

Somlyai et al. showed in a clinical prospective study in human volunteers with pre- or manifest diabetes that DDW (104 ppm) significantly decreases fasting glucose levels and reduces insulin resistance (Somlyai et al., 2020).

4 Promising new areas

4.1 Long term memory

Mladin et al. found in normal rats that deuterium-depleted water (27–30 ppm) in comparison to normal water

(145–150 ppm) significantly decreased the number of reference memory errors, speculating that DDW may stimulate long-term memory (Mladin et al., 2014).

4.2 Anti-aging effect

Avila et al. showed in *Caenorhabditis elegans* (*C. elegans*) that DDW (90 ppm) reversed manganese (Mn)-induced lifespan decrease, restoring lifespan (Avila et al., 2012).

4.3 Sports performance

Boros et al. reported that after six failed attempts by the same high altitude professional mountain climber using carbohydrate-based nutrition (glycogenic), the athlete in deuterium depleting nutritional ketosis was finally able to summit Mount Everest without supplemental oxygen (Boros et al., 2024).

5 Discussion

The findings from animal studies indicate that deuterium depletion prevented tumor development and prevented the expression of cancer-related genes. This data further highlights smaller tumor volume and smaller tumor weight. Additionally, deuterium depletion shows a counteraction of a depressive-like state. Findings also show reduction in blood glucose levels. Deuterium depletion in mice simulated improved long-term memory. Anti-aging was demonstrated.

Deuterium depletion in humans showed delayed progression of prostate cancer. Deuterium depletion also showed improved mean survival time in lung cancer, glioblastoma multiforme, certain subgroups of breast cancer patients, small cell and non-small cell lung cancers, and advanced pancreatic cancer. In addition, deuterium depletion was associated with absence of relapse in cancer patients. Furthermore, fasting glucose levels and reduced insulin levels were found in deuterium depleted individuals with pre or manifest diabetes. Increase in sports performance was also exhibited.

This scoping review has some limitations. Some of the studies included were in vivo, in vitro, and animal models; which can make difficult to translate these outcomes into humans. Also, the findings indicate a majority of research focusing on cancer. Furthermore, this scoping review's results are from a small number of studies and only one randomized controlled trial, which limits the ability to confirm cause and effect. There was limited information available on anti-aging, therefore at this time, any evidence is lacking, and more research is needed. Although there was one study available on sports performance, this area is promising. There is abundant space for further research to establish more about deuterium depletion and its effect on human health using natural disease related variations in D/H in reference with environmental water (Gharibi et al., 2022; Maloney et al., 2024).

To summarize the main findings, deuterium possesses profound biological effects, and deuterium depletion has major roles for example: in the prevention of cancer development with various anticancer effects, it lowers the rates of depression, reduces circulating glucose in diabetes, stimulates long-term memory, increases lifespan, and enhances sport performance.

6 Conclusion

Due to the limited information currently available on deuterium, existing knowledge in the field and mapping of research was done in this area. Therefore, this review examined the evidence regarding nutritional deuterium depletion related to the results of cancer prevention, cancer treatment, depression, diabetes, long-term memory, anti-aging, and sports performance and concluded a positive impact. The positive results were consistent, even with limited number of studies and study designs currently available. It can be concluded that nutritional deuterium depletion can and should be proposed for future studies and high-quality research priorities, especially in more human studies, to determine further efficacy along with potentially broad medical indications. Fundamental mechanisms regarding the active involvement of compartmental, inter- and intramolecular deuterium disequilibrium in adaptive biology, i.e. disease development, in the human deutenome have recently been summarized in a review article (Boros et al., 2024). Due to their importance, readers may also review single protium-deuterium exchange reactions involved in DNA chemistry on the occurrence of open states for additional mechanisms via genetic regulation of biological processes by deuterium (Dzhimak et al., 2018). Overall, the data analysis supports that deuterium depletion through deuterium-depleted water and a deuterium-depleted diet (natural ketogenic) has an impact on health.

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Data availability Data is provided in supplementary information files, where results were extracted from, as described and referenced in the text of this article as citations.

Declarations

Conflict of interest The author(s) declare that there is no conflict of interest.

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