Review Article

Impact of high-salt diet in health and diseases and its role in pursuit of cancer immunotherapy by modulating gut microbiome

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Abstract

Cancer chemotherapy remains an area of concern, as many of the therapies are uncomfortable involving side effects and unpleasant experiences. These factors could further reduce patient's quality of life, and even endanger their life. Many therapeutic strategies have been tried to reduce the unpleasant side effects and increase the treatment effectiveness; however, none have shown to have promising effects. One of the main hindrances to cancer therapy is the escape strategies by tumor cells to the immune attack. Promoting inflammation in the tumor microenvironment is the cornerstone and key therapeutic target in cancer chemotherapy. High-salt diet (HSD) intake, though it has deleterious effects on human health by promoting chronic inflammation, is found to be advantageous in the tumor microenvironment. Studies identified HSD favors an increased abundance of *Bifidobacterium* species in the tumor environment due to gut barrier alteration, which, in turn, promotes inflammation and favors improved response to cancer chemotherapy. A review of the literature was carried out to find out the effects of an HSD on health and diseases, with special mention of its effect on cancer chemotherapy. Studies emphasized HSD would block the myeloid-derived suppressor cells which will enhance the tumor immunity. Exploration of the precise mechanism of simple HSD regime/ingestion of specific bacterial species as probiotics will be effective and essential to formulate the game-changing cancer chemotherapy. With the modern era of healthcare moving toward precision medicine where the physician can choose the treatment option suitable for the individual, HSD regime/ingestion of specific bacterial species can be considered.

Keywords: Anti-tumor activity, chronic inflammation, gut dysbiosis, high-salt diet, immuno-inflammation, tumor immunity

Introduction

Salt is an essential part of our diet; we consume salt in the form of sodium chloride where 40% is sodium and 60% is chloride. Salt is required for maintaining normal electrolyte balance, excitation of nerves, contraction of muscles, and absorption of nutrients. Apart from sodium and chloride often salts are fortified with iodine and/or vitamin A to meet the unmet requirements of

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these essential nutrients.[1] Salt has been used for thousands of years by humans as a preservative in foods that have to be stored for a long duration. High salt concentrations help to prevent bacterial growth and prevent food from spoiling. Adding extra salt to food is unnecessary, as some foods already contain natural salts. The habit of enhancing the taste of food with extra salt can have detrimental effects. There is an increase in salt intake observed in all adults, that is, >2 g/day. According to the recent food and drug administration (FDA) guidelines, sodium intake of <5% of daily value is considered low and >20% of daily value is considered high.[2] The World Health Organization (WHO) also recommends a daily intake of salt of <5 g in adults to reduce the risk of heart attacks, cardiovascular diseases, and stroke.[3]

Salt increases the palatability of food, commonly used in excess amounts in most fast foods. Moreover, it is used in excess amounts in tinned and canned foods.[4] The recent shift toward westernization of diet aids high salt consumption because by default western diets will have high salt content.[5,6] Though it is indispensable, a high-salt diet (HSD) can have harmful effects.[7] HSD causes high blood pressure, cardiovascular diseases, chronic inflammatory diseases, autoimmune diseases, stroke, and even increases the risk for some cancers.[8,9] HSD is known to increase sympathetic activity and can cause vasoconstriction, which can result in hypertension.[10,11] HSD by altering the gut microbiota, induces a change in the short-chain fatty acid production, which is believed to be proinflammatory leading to chronic inflammatory diseases.[12] HSD favors the differentiation of immunogenic T cells to proinflammatory Th17 cells triggering autoimmune diseases.[13] The proinflammatory state evoked by HSD has a proven effect on the tumor microenvironment by clearing the hurdle in cancer immunotherapy. The harmful effects of high salt are well recognized by primary care physicians, but the beneficial effects of a high-salt diet are not well known among family physicians. Hence, we tried to address both the harmful and unknown beneficial effects of HSD, as a double-edged sword in this narrative review.

Materials and Methods

A review of the literature was carried out in PubMed and Scopus about the impact of an HSD on health and diseases and its role in cancer immunotherapy by modulating gut microbiome. The articles were selected consciously from March 2009 to November 2023. Alteration of bacterial taxa due to an HSD in a rodent model and the disease associated are compiled and discussed in Table 1. The importance, relevance, and future perspective are discussed in the study.

Impact of high salt intake on human health

HSD and its predisposition to cardiovascular disease are well recognized.[14] Several available studies and meta-analyses confirm the association between higher dietary salt and cardiovascular disease mortality and morbidity.[15,16] The increased salt content in the diet ultimately increases the blood sodium levels, which causes water retention to bring about fluid overload and increases sympathetic activity, which may result in fatal health effects in cardiac and renal failure patients.[17] In view of this, the WHO recommends restriction of salt intake to less than 5 g per day[18] [Figure 1].

Salt, apart from the cardiovascular complications, was also found to predispose to immune-mediated inflammatory diseases.[19] Although immune cells have a protective and preventive role against various pathogens invading the host, their aberrant stimulation can be harmful.[20] Jantsch *et al.* showed that high salt concentrations in skin lesions infected by bacteria have a better anti-microbial defence. They demonstrated that high salt concentration in the skin lesions activates proinflammatory macrophages (M1) through the p38/MAPK (mitogen-activated protein kinase) signalling pathway and the same can be replicated endogenously, suggesting high salt can aid in removing the infections efficiently.[21] Kleinewietfeld *et al.* demonstrated the differentiation of T cells to pathogenic TH17 cell subtype under the high salt environment in a mouse model study.[22] They also explored the underlying pathways for the activation of TH17 cells under high salt concentrations and found the underlying NFAT5 (nuclear factor of activated T cells 5), SGK1 (serum and glucocorticoid regulated kinase 1), P38/MAPK signalling pathways were involved in the downstream process. Induction of Th17 cells under the high salt concentration stimulates the stable production of inflammatory cytokines such as interleukin (IL)-6, IL-8, IL- 17, IL-22, and tumor necrosis factor α (TNF-α), which are found to be harmful mediators in chronic inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease, and psoriasis.[23] HSD activates the inflammatory cells and causes the deposition of inflammatory cells at various tissue sites, leading to chronic inflammation.[24] Maifield *et al.* demonstrated that the lesions from the patient with psoriasis show high sodium content and increased deposition of inflammatory cells, particularly Th17 cells. The salt content is found to directly reflect the disease severity in psoriasis as assessed by the PASI (psoriasis area and severity index) score.[25]

Clinicians encountered a recent increase in the incidence of autoimmune diseases,[26] which could be attributed to environmental changes, diet modifications, genetic influences, etc., Among the various risk factors, dietary factor (HSD)

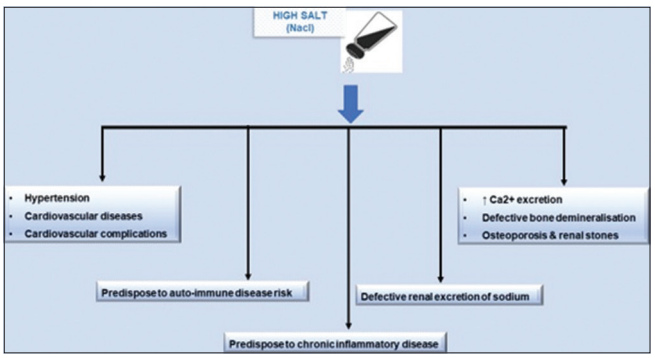

Figure 1: Effect of high dietary salt intake on human health

Table 1: Alteration of bacterial taxa due to high-salt diet in a rodent model and the associated disease

Study by	Increased/decreased	Phylum/class	Family/genus	Disease/associated metabolite
Ibrahim Hamad *et al*,[48] 2022	Increased	Firmicutes/Clostridia	*Anaerostipes*	Inflammatory bowel disease
		Bacteroidetes	*Alistipes*	
		Verrucomicrobiae	*Akkermansia*	
	Decreased	Actinobacteria	*Bifidobacterium*	
		Bacillota	*Faecalibaculum*	
		Bacillota	*Blautia*	
		Firmicutes/Bacilli	*Lactobacillus*	
Guo Qing *et al*,[49] 2021	Increased	Proteobacteria	Proteobacteria	Non-alcoholic fatty liver disease (NAFLD)
		Bacteroidetes	Bacteroidetes	
Kazi Farhana Afroz *et al*,[42] 2021	Increased	Verrucomicrobiae	*Akkermansia*	Autism spectrum disorder, Cognitive dysfunction
		Firmicutes/Bacilli	*Lachnospiraceae/Roseburia*	
	Decreased	Firmicutes/Bacilli	*Lactobacillus*	
		Proteobacteria	Proteobacteria	
		Bacteroidetes	Bacteroidetes	
Magne F *et al*,[51] 2020	Increased	Firmicutes	Firmicutes	Obesity
Bier *et al*,[12] 2018	Increased	Actinobacteria	*Corynebacteriaceae*	Hypertension
		Firmicutes/Clostridia	*Christensenellaceae*	
		Proteobacteria	*Erwinia*	
	Decreased	Firmicutes/Clostridia	*Anaerostipes*	
Miranda *et al*.[53] 2018	Decreased	Firmicutes/Bacilli	*Lactobacillus*	Colitis
Wilck *et al*.[54] 2017 Petta *et al*.[55] 2018	Increased	Bacteroidetes	*Prevotellaceae*	Hypertension, Autoimmune encephalomyelitis Multiple sclerosis
		Bacteroidetes	*Alistipes*	
		Burkholderiales	*Parasutterella*	
		Verrucomicrobiae	*Akkermansia*	
	Decreased	Actinobacteria	*Rothia*	
		Firmicutes/Clostridia	*Johnsonella*	
		Firmicutes/Bacilli	*Lactobacillus murinus*	
Wang *et al*,[56] 2017	Increased	Firmicutes/Bacilli	*Lachnospiraceae/Roseburia*	Impact on protein digestion
		Firmicutes/Clostridia	*Ruminococcus*	
		Firmicutes/Clostridia	*Oscillibacter*	
	Decreased	Firmicutes/Bacilli	*Lactobacillus*	
		Bacteroidetes	*Alistipes*	
Hu Jingjuan *et al*,[59] 2017	Increased	Bacteroidetes	Bacteroidetes	Crohn's disease, Kidney injury, hypertension
	Decreased	Firmicutes	Firmicutes	
Cuevas-Ramos *et al*.,[60] 2010	Increased	Proteobacteria	*H pylori*	Colorectal cancer
Diaz *et al*.,[61] 2018	Increased	Proteobacteria	*H pylori*	Gastric cancer

directly induces the change in gut microbiota, which favors an inflammatory state affecting immune homeostasis, which is found to be the major driving force towards autoimmune diseases.[27] Although research has explored the possibility of environmental influences like infections, pollution, stress, and dietary choices triggering lupus, none have emerged as definitive contributors to the disease. Recently, HSD was found to promote the disease severity and episodes of nephritis in lupus patients.[28,29] In A study conducted in an experimental encephalomyelitis model of mice with multiple sclerosis (MS), high salt was found to increase the disease activity and exacerbate the symptoms associated with MS.[30,31] Increased disease activity and the relapse rate were found in a cohort of 70 relapsing-remitting multiple sclerosis patients (RRMS), who had high sodium intake, followed over 2 years.[32] Chron's disease and ulcerative colitis start primarily, as a disease-causing inflammation of the lining epithelium of intestinal mucosal cells and later progress to life-threatening auto-immune disease.[33] In inflammatory bowel disease (IBD), HSD depletes anti-inflammatory lactobacillus and favors an inflammatory environment by favoring the differentiation of T cells toward inflammatory Th17 cells, which exacerbate episodes in IBD.[34] In a large cross-sectional study by *Bae et al.,* they found that patients with rheumatoid arthritis (RA) excrete more sodium in the urine. They concluded by stating high dietary sodium is an independent risk for RA and recommends the reduction of salt intake.[35] Several studies have found a similar association and recommend the reduction of dietary salt in RA.[36-38]

Risk factors for cancer development such as dietary factors, environmental changes, pollutants, and genetic factors (obesity), [39-42] are almost associated with the state of chronic inflammation.[43] However, once the cancer state is established, tumor cells tend to evade the inflammation as their defense mechanism against immune attack. Inducing inflammation at the tumor site is a major stumbling block to finding an effective anticancer drug.[44] Though the state of

inflammation has deleterious effects,[45] this property of high salt and activation of immune cells in the tumor microenvironment can be utilized to aid effective treatment options against the tumor. Moreover, salt-induced changes in the gut microbial flora were also found to have an effective role in the destruction of tumor cells.[46]

Effect of HSD on gut microbiota and its implication in health and diseases

The gut microbiome, recognized as an independent metabolic organ, has emerged as a crucial factor in determining human health and disease.[47] A decade of research shows that an HSD has diverse effects on gastrointestinal tract (GI) function and gut microbiota, which leads to many clinical diseases such as hypertension, inflammatory bowel disease, colitis, autism, non-alcoholic fatty liver disease, neurodegenerative disease, and gastric cancer [Table 1].[48-61] Surprisingly, an HSD proved to slow down tumor growth and enhance anti-tumor activities. Promising results were proven in *in vivo* animal studies in cancer prevention and treatment.

High salt diet–gut microbiome-anti tumor property

Though HSD has been associated with many diseases due to gut dysbiosis, recently it is gaining utmost importance because of the anti-tumor properties shown by HSD. A recent experimental study by Risvi *et al.*[46] showed that HSD-fed B16 cells implanted (B16F10 skin melanoma) mice had an increased abundance of *Bifidobacterium*, which led to colonic tumor suppression by upregulating natural killer (NK) cell frequency and downregulating NK cell inhibitory signals (mainly programmed cell death 1 molecule) through marked upregulation of serum hippurate. He also demonstrated that HSD-fed mice showed increased gut permeability resulting in intertumoral localization of *Bifidobacterium,* which had crosstalk with NK cells for its activation through hippurate. Studies showed that *Bifidobacterium* administration as a probiotic is found to destroy the tumor cells and increase the effectiveness of anti-cancer therapy.[62] Shimuzu *et al.*[63] also found a significant decrease in tumor growth in the breast tissue of a mouse model following the administration of a recombinant *Bifidobacterium longum*. This suggests probiotic administration as an adjuvant to the therapy could be a possible chemotherapeutic target to increase the efficiency of therapy.

In contrast to the previous study results by Risvi *et al. and* Hwang Soonjae *et al.*, a study by Janakiraman Mathangi *et al.* showed that HSD-fed acute myeloid leukemia (AML) cells implanted mice did not influence tumor progression. He also emphasized that HSD-induced anti-tumor activity is type-specific as these were noted in barrier sites such as the skin and intestine (against melanoma and colonic tumors).[64]

Precise mechanism of tumor immunity in HSD

Following the warning by the WHO on reducing dietary salt intake, the usage of salt has been reduced drastically in most fast foods.[65] Recently, high salt concentration in cancer tissues was found to have anti-tumor activity. The precise mechanisms are illustrated in Figure 2.

1. Colonization of *Bifidobacterium* at tumor microenvironment:

Numerous factors were responsible for maintaining gut integrity from individual dietary factors to disease states. A recent study showed that the rats fed with high dietary salt disrupted the integrity of intestinal mucosa when compared with rats fed with normal dietary salt and there was a two-fold increase in *Bifidobacterium* in the tumor tissue site, which confirms the possibility that the HSD disrupts the intestinal mucosal barrier and leads to increased *Bifidobacterium* species at the tumor site. The presence of bacteria in the human tumor tissue site was confirmed in a human study by *Nejman et al.,* they demonstrated the presence of bacterium species in 1,010 human tumor samples taken from the sites exposed to the external environment and non-exposed sites.[66] The characterization of the bacterial species was performed by *Heymann et al.*, and they found the presence of common bacterial species present in the tumor site.[67] Later, Sivan *et al.* identified the bacterial species as *Bifidobacterium* by sequencing 16S rRNA. This confirms the presence of *Bifidobacterium* at the tumor site.[68] A metagenomic study also confirms the abundance of *Bifidobacterium* in HSD-fed mice when compared to control mice, fed with a normal diet.[69]

2. Activation of immune cells in the tumor microenvironment:

Immune response to the infection starts and the innate immune cells, primarily NK cells, identify the pathogen; it may be cancer cells/bacteria and kill it.[70] During this process, several inflammatory mediators and bacterial degradation products will be released, which will recruit more inflammatory cells to the site and cause inflammation. NK cells identify and destroy the pathogens by releasing various inflammatory cytokines, particularly interferon gamma (INF-γ). INF-γ recruits inflammatory T cells, macrophages, and dendritic cells.[71] The immune mediators released by NK cells recruit and activate T cells in the tumor tissue site. T cells recognize the foreign antigen

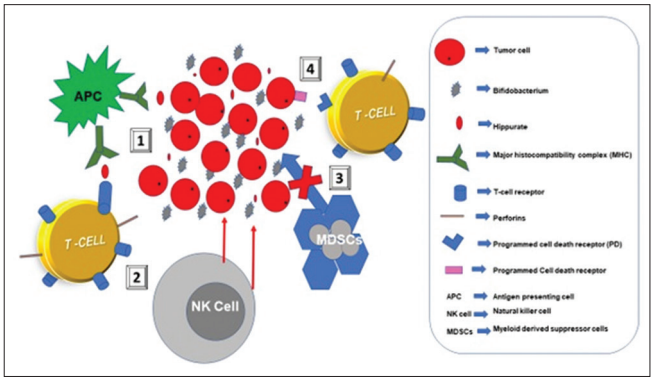

Figure 2: High salt diet and its role in tumor immunity. 1. Colonization of *Bifidobacterium* at tumor microenvironment, 2. Activation of immune cells in the tumor microenvironment, 3. Inhibition of myeloid-derived suppressor cells (MDSCs), 4. Immune evasion and increasing efficacy of tumor immunotherapy

using a major histocompatibility complex (MHC) and attack both the bacteria and tumor tissue. T cells also identify and bind hippurate present at the site, which is released as a degradation product of cancer cells, also from the bacteria.[72] The activation of T cells causes the release of inflammatory cytokines such as IL-1, IL-6, IL-10, IL-5, INF-γ, and TNF (IL-interleukin, INF-interferon, TNF-tumor necrosis factor). Inflammatory mediators cause tissue destruction and apoptosis of the cancer cells by inducing intracellular apoptotic genes.[73]

A recent *ex vivo* study performed on breast cancer-bearing C57B1/6 mice showed HSD activated and caused the expansion of tumor-primed cytotoxic CD4+ lymphocytes, which exert anti-cancer activity.[74] Moreover, the high salt concentration at the tissue site is known to induce differentiation of T cells to inflammatory Th17 cells to cause add-on tissue inflammation and tissue destruction.[75] Perforin-expressing cells such as T and NK cells destroy the cancer cells by creating a pore in the cell surface of tumor cells.[76] The cumulative effect added on by high salt concentration leads to effective tumor destruction.

3. Inhibition of myeloid-derived suppressor cells (MDSCs)

Myeloid cells support the growth of the tumor by providing necessary growth factors such as vascular endothelial growth factor (VEGF) and can cause immunosuppression.[77-79] The stimulus for the production of myeloid cells occurs in the bone marrow by inflammatory cells.[80] Willebrand *et al.*, in the murine model, found that the HSD would block the myeloid-derived suppressor cells (MDSCs), thereby enhancing anti-tumor immunity.[81] Along similar lines, He *et al.*, propounded that the MDSC clusters differentiate into two different antitumor phenotypes, namely, the anti-tumor macrophages (from monocytic-MDSCs) and those acquiring pro-inflammatory functions (from granulocytic-MDSCs) on exposure to high salt concentration. Subsequently, HSD can inhibit tumor growth in mice by regulating MDSC differentiation.[82]

4. Immune evasion and increasing efficacy of tumor immunotherapy:

The programmed cell death (PD) receptor, which is present on T cells, binds to the cancer cells and causes their apoptosis. Tumor cells can produce programmed cell death receptor protein L1 (PD-1) which binds to the PD receptor and inactivates T cell, this is one of the tumor evasion mechanisms by tumor cells.[83-85] Immunotherapy against PD-1 to restore T cell function has been successfully identified and used, but a significant number of patients do not respond to PD1 inhibition because the function depends on the tumor cell's ability to produce PD1 protein.[86] Hence, there is a need to identify a biomarker to indicate patient responsiveness to anti-PD1 therapy. Haete *et al.* found that patients with increased hippurate levels respond well to anti-PD1 therapy. This may be because of increased tissue destruction due to anti-PD1 therapy and hence increased hippurate levels or salt-induced increased hippuric acid levels increase the anti-tumor activity and reduce the dose of anti-PD1 immunotherapy.[87]

In contrast, Janakiraman *et al.* concluded though the exposure to HSD in mice resulted in changes in microbiota composition, TH17 responses, and NK cells, the same did not influence tumor development (AML). Hence, the type of tumor would determine the effect of HSD on tumor immunity.[88] Similarly, HSD was found to promote the progression of breast cancer and lung metastasis via the Th17 lymphocytic responses in a mice model study.[89]

Conclusions

Consumption of an HSD is considered an unhealthy lifestyle due to its association with chronic inflammation, cardiovascular diseases, and autoimmune conditions. There is a shift of the immune system toward the promotion of proinflammatory effects such as TH17 and M1-like macrophages and functions of anti-inflammatory cells, such as M2-like macrophages and impairment of regulatory T cells. However, this untoward side effect is found to be beneficial in tumor immunity.

HSD increases the permeability of the gut, favoring the entry of *Bifidobacterium* to the tumor site to stimulate the NK cells and activate the T cells to cause the destruction of tumor cells and increase the hippurate levels. Tumor cells evade the destruction by programmed cell death receptor protein L1, which binds to the PD receptor and inactivates T cells. Even though anti-PD1 therapy restores the T cell function, it is not effective in all tumors due to the PD1 secretory function of some tumors. This can be circumvented by measuring the hippurate levels, which can guide the effectiveness of anti-PD1 therapy. The high salt environment provides an avenue to avoid the checkpoint inhibition by tumor cells by interfering with the immune-mediated inflammation, which can be utilized as the treatment modality by modulating the salt level. To conclude, an HSD is a double-edged weapon but has a promising role in tumor immunity by influencing gut microbiome and other bacterial products, which need further research to uncover its potential benefits.

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Conflicts of interest

There are no conflicts of interest.

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