

## Research Article

# Etiology of Chronic Disease: A Discussion on Epstein-Barr Virus

Elyn Jacobs\*

*Elyn Jacobs Consulting, Inc., New York, USA*

### Abstract

Epstein-Barr Virus (EBV) is a common human herpes virus and is one of the most common and prolific viral infections in humans. Over 95% of adults carry this virus, and most children are infected as well. Chronic disease is the clinical manifestation of primary infection with Epstein Barr virus. Infection with EBV is often asymptomatic. But once the virus inserts itself into immune B cells, it reprograms them, effectively evading programmed cell death and escaping recognition and destruction by cytotoxic T cells. EBV can manifest in a range of pathologies including various cancers, Infectious Mononucleosis (IM), autoimmune disorders, chronic fatigue syndrome, thyroid disease, meiners disease, type 1 diabetes, Lyme disease, and numerous other conditions.

Deactivation of the virus is critical. New antiviral therapies and an effective EBV vaccine might protect against the wide range of pathologies from infectious mononucleosis to various cancers. Dendritic cell therapy may also be effective. More research needs to be done that these areas. At this time, no EBV vaccine has been approved for use. Until a vaccine or other medical intervention is made available, strategies aimed at deactivating the virus and preventing re-activating of the virus should be emphasized and public awareness increased, particularly among those diagnosed with a chronic disease. Natural solutions currently available are high dose vitamin C and D therapies as well as antiviral agents such as olive leaf extract, licorice root, coconut, astragalus, bee propolis, lysine, and zinc.

**Keywords:** Antiviral therapy; EBV; EBV vaccines; Herpes virus

\*Corresponding author: Elyn Jacobs, Elyn Jacobs Consulting, Inc., New York, USA, Tel: +1 9179030775; E-mail: elyn@elynjacobs.com

**Citation:** Jacobs E (2018) Etiology of Chronic Disease: A Discussion on Epstein-Barr Virus. J Cancer Biol Treat 5: 014.

**Received:** April 28, 2018; **Accepted:** June 02, 2018; **Published:** June 16, 2018

**Copyright:** © 2018 Jacobs E. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Introduction

The biology of the Epstein-Barr Virus (EBV), the diseases it precipitates, the nature of the virus-host interaction, and the limited awareness of managing EBV infections by the general medical community are the subjects of this review. A brief overview of solutions will be presented.

Scientists have known for over 50 years that the Epstein-Barr virus can interact with human DNA, significantly raising the risk of many major diseases. However, it is only in the past five to ten years have we started to understand some of the possible mechanisms of how EBV may lead to long-term health complications. As such, the impact of this association is largely overlooked at the physician-patient level. As the research mounts the connection of virus to chronic diseases will hopefully become part of medical school curriculum. Meanwhile, because of the overwhelming connection of EBV to many, if not most, chronic diseases, it is imperative that general practitioners as well as specialists such as oncologists, nephrologists, endocrinologists, and others become more educated on the far-reaching ramifications of EBV.

This review summarizes potential resources exhibiting antiviral activity. Vaccines are at the forefront of clinical interventions, but effective ones have proven to be elusive. Potentially, an EBV vaccine that induces, regulates, and maintains T-cell immunity could be helpful. Antiviral pharmaceuticals have also proven to be ineffective. EBV is no doubt a challenging entity, and although there has been much work done more needs to be done. In the meantime, given the well-studied and documented correlation between this virus and oncogenetic and other events and the lack of safe and effective medical interventions, natural substances that demonstrate antiviral activity should be given consideration. I have not attempted to be exhaustive but have provided an overview of how natural substances can be helpful in the deactivation of EBV, and thus have a significant impact on the devastating implications of this virus. This author recognizes that further studies and clinical trials may be needed to prove the efficacy of natural substances, but these may not be forthcoming for financial reasons.

### Overview of Epstein Barr Virus

Along with herpes, shingles, and chicken pox, EBV is part of the herpes virus family. Over 95% of adults worldwide harbor lifelong latent EBV infection. Most children are infected as well, and often presents in teens as Infectious Mononucleosis (IM). Once a person is infected with EBV, it remains dormant in the body, often asymptomatic. For some, this will not be a problem. For others, it can result in life-threatening, long-term consequences.

Scientific findings suggest that EBV infection drives the activation of genes that contribute to an individual's risk of developing various disease conditions. Once the virus inserts itself into a specialized immune lymphocyte (B cell), it hijacks the DNA to take control of the cell. Essentially, EBV invades B cells, re-programs them, and changes

the way they function. If not deactivated, the virus will continue to modify the host's DNA, disrupting the critical process of apoptosis (programmed cell death). Unfortunately, EBV often evades recognition and destruction by T cells. In patients who have impaired T-cell immunity and are unable to control the proliferation of EBV-infected B cells, the virus will then provoke various disease conditions.

EBV is the primary cause of infectious mononucleosis. It is also well established that many cases of Chronic Fatigue Syndrome (CFS) follow an acute viral infection. Other conditions that are EBV-related include various cancers, such as Hodgkin's lymphoma [1], non-Hodgkin lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma [2], breast cancer [3], prostate cancer [4], colon cancer [5], and most others. EBV is also strongly linked to autoimmune disorders such as Multiple Sclerosis (MS), lupus, Hashimoto's, rheumatoid arthritis, and Graves' disease [6]. Thyroid disease, Meiners disease [7-11], type 1 diabetes [12], Lyme disease [11], Inflammatory Bowel Disease (IBD), celiac, and numerous other conditions can be added to this list.

## Biology of Epstein Barr

Epstein-Barr is an opportunistic human pathogen that causes a significant number of diseases in immunocompromised hosts. Pathogens can directly or indirectly result in numerous cancer and non-cancer related events. Viral mechanisms for which disease can result include gene instability, increased cell proliferation, and avoidance of apoptosis. These mechanisms are also involved with DNA repair processes and evasion of the antiviral immune response [13]. Specific immune cells known as CD8+T cells are needed to fight EBV. If there is a genetic or otherwise deficiency present, this presents an uncontrolled environment for EBV. Some individuals have a genetic predisposition to low levels of CD8+T, but these cells also tend to decline with age. Diminished CD8+T cells are particularly common in people with low vitamin D levels [14]. This makes sense as vitamin D is a direct and indirect regulator of T cells and is an important regulator of immune function. Importantly, T cells contain more vitamin D3 receptors than any other immune cell. The Vitamin D Receptor (VDR) regulates the expression of more than 900 genes involved in a wide array of physiological functions, including immunity. The impact of VDR signaling on immune function has been the focus of many studies as a link between susceptibility to infections and diseases [15,16]. T cells express the VDR and have been shown to be direct and indirect vitamin D targets. The expression of these receptors is necessary for the development of natural killer cells as well as CD8+T cells [17].

As mentioned, exposure to EBV during the teen years often results in infectious mononucleosis. Teenagers are more susceptible to IM and other EBV-related issues than younger children. This may be for two reasons. First, CD8+T cells begin to decline dramatically by that age, and second, teens are often less likely to spend as much time in the sun (year-round) as their younger counterparts, potentially lowering vitamin D levels. Higher vitamin D concentrations appear to correlate with lower EBV antibody levels (more about the role of vitamin D below).

## Clinical Manifestations of EBV

Epstein-Barr Virus (EBV) has been suspected of involvement in the pathogenesis of various chronic autoimmune diseases since as early as 1971 [14]. However, at that time and in years forward, the

mechanisms by which the virus triggered disease were not clear. It is only recently that researchers have been able to gain a better understanding of EBV, but the dilemma of clinical forms of EBV infection is still far from resolved. Since there is a wide variety of a clinical syndrome with which EBV infection has been linked, it is extremely difficult to identify a univocal pathogenetic link. However, considerable and mounting evidence shows that EBV is directly linked to numerous diseases, with increasing clarity. For example, EBV is one of the most frequently considered environmental factors involved in autoimmunity. Nearly all anaplastic nasopharyngeal carcinomas contain EBV DNA in the tumor cells. Further, about 9% of gastric carcinomas are associated with EBV and 90% of gastric lymphoepitheliomas are EBV positive. New research suggests that celiac, along with IBD, may be caused by EBV's ability of EBNA2 and its related transcription factors to affect regulatory genes associated with autoimmune disorders [18]. While this author cannot list every scientifically referenced association between EBV and particular chronic diseases, below are a few relevant early studies. I present these studies simply to help the reader to understand that EBV and its connection to disease has been studied and documented. Hopefully these samples give the reader a sense of the gravity of EBV.

- A 1996 study published in *Seminars in Cancer Biology* found EBV in most cases of gastric carcinoma, implicating EBV as one of the contributing factors to the development of gastric cancer [19].
- 2010 research done at the School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, Australia, found a significant association between EBV and breast cancer. They identified 27 published studies concerning EBV in breast cancer.
- 2013 research published in *Future Virology* acknowledged that EBV is implicated in both Multiple Sclerosis (MS) and lupus [20].
- 2013 findings published in *Clinical & Translational Immunology* linked dysregulation by EBV in B-cells to the evasion of the immune defense and found EBV to be the likely initiator of autoimmune disorders and the progression of these diseases [21]. These researchers concluded that EBV is an environmental trigger in the development of systemic autoimmune diseases.
- 2014 research published in *Clinical and Translational Immunology in Nature.com* clearly stated that EBV is the primary cause of mononucleosis and is associated with several cancers. They also found EBV to be associated with autoimmune diseases, including MS. They discovered that the mean time between EBV infection and the development of MS was about 6 years [22].
- 2014 research found a strong association between EBV and breast cancer in Sudanese patients as well as considerable epigenetic silencing of tumor suppressor genes that correlate with viral oncogenesis [23].
- Iranian research published in 2014 in the *Journal of Paramedical Sciences* found that in patients with colorectal cancers, Epstein-Barr DNA was found in 60% of tumor samples.

## Recent Studies

A 2016 study published in the *Central European Journal of Immunology* found a possible link between EBV and autoimmune thyroid disorders and concluded that while EBV is not the only agent responsible for the development of these conditions, it can be considered

a contributory factor [24]. The researchers detailed the role of EBV in autoimmunization, citing the following: The virus is a common pathogen responsible for the worldwide prevalence of autoimmune diseases; EBV stays in the body throughout life, and the virus modifies the host immune response [25]. That same study reported that EBV shows immunomodulatory and oncogenic effects. It encodes the *bcl-2* oncogene that inhibits apoptosis and interferon signaling in B-cells and is responsible for changes in the production of pro-inflammatory cytokines, such as Interleukin 10, which intensifies *bcl-2* expression.

In a study published in *EBioMedicine* in 2016, researchers led by Gerbury Wulf, MD, Ph.D, of the Hematology/Oncology Division at Beth Israel Deaconess Medical Center, reported that EBV may accelerate the development of malignant breast cancer. The researchers found that breast cells bonded to EBV and that the virus lowered the threshold for transformation into a particularly aggressive form of cancer. They suspected that if a young woman is infected with EBV during her teenage years, her epithelial cells could be exposed which could leave genetic scars that could facilitate breast cancer formation [3]. This is notable as many scientists believe that EBV leads to changes in gene expression, activation of oncogenic signaling, and increases the risk of cancerous transformation. In this case, it was determined that EBV-related gene expression changes are associated with high grade cancers, which tend to have a worse prognosis. The recommendation was a childhood vaccine against EBV.

In 2017, researchers at the German Cancer Research Center sought to find out how the virus reprograms cells into becoming cancer cells. They found that a component of the EBV protein interferes with cell division and increases the risk of cancer development. Their research also led them to believe that EBV could cause the development of additional tumors, even if those tumors were not originally generated as a result of the virus. They concluded that “we must push forward with the development of a vaccine against EBV infection. This would be the most direct strategy to prevent an infection with the virus. Our latest results show that the first infection could already be a cancer risk and this fits with earlier work that showed an increase in the incidence of Hodgkin’s lymphoma in people who underwent an episode of infectious mononucleosis [26]”. Again we are reminded that the virus is significantly involved in the development of cancer, and that interventions are necessary, potentially a vaccine.

A recent study conducted by scientists at Cincinnati Children’s Hospital Medical Center published in *Nature Genetics* linked EBV to seven major diseases. These include lupus, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, celiac disease, and type 1 diabetes. The researchers also found associations with 94 other conditions. They acknowledged the connection to mononucleosis as well as the likelihood that further studies would likely find that EBV is involved in many other diseases, perhaps as many as two-hundred. Notably, the team first found that a viral protein called EBNA2 was associated with almost half of the genetic regions associated with lupus. EBNA2 works through human transcription factors, which bind to DNA and affect the expression of genes. The team then found that EBNA2 binds to regions associated with multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis, and celiac disease. Importantly, these authors pointed out that the impact of the virus could differ among various diseases. This could lead to cures, but many things are yet unknown,

which could result in the need for more than one therapy for intervention. John Harley, MD, Ph.D, Director of the Center for Autoimmune Genomics and Etiology at Cincinnati Children’s and one of the lead scientists in the study, commented that “I’ve been a co-author in almost 500 papers. This one is more important than all of the rest put together. It is a capstone to a career in medical research [27]”. If Harley is correct, then EBV may well find itself as a major topic in medical schools throughout the world, producing a new generation of doctors who will recognize the importance of EBV in the diagnosis, and treatment of the disease.

## Deactivating EBV: Current and Future Therapies

### Vaccines

Scientists have been looking at vaccines to combat EBV for many years. Reminding the reader that IM is not always a benign disease, a vaccine that could prevent mononucleosis would be useful, and certainly one for EBV. Unravelling the mechanisms of virally-triggered cell transformation has been an enormously complex task and has thus far mostly eluded resolution. In a review done by the Division of Biomedical and Clinical Laboratory Sciences, Edinburgh University Medical School, researchers concluded that “a vaccine to prevent EBV infection would not only have the potential to relieve the world of a substantial cancer burden but could also provide definitive proof of an essential role for the virus in human aetiology [28]”. Researchers studying vaccine attempts believe scientists are getting closer to creating one that is both safe and effective. The problem may be that the characteristics of the virus are complex and vary greatly, which has made it difficult to create a single vaccine. It does not appear to be the microbes causing problems so much as the disruption of the host’s immune functions that allows pathogens to flourish, thereby complicating the options for intervention. Notably, studies show microbes slow down immune reactivity by dysregulating the VDR, presenting a survival mechanism for the virus. Most efforts to develop prophylactic vaccines have focused on EBV gp350, which is the major target of neutralizing antibody. A 2015 study found that the promising gp350 vaccine might reduce the incidence of infectious mononucleosis. It referenced a single phase 2 trial of an EBV gp350 vaccine. The vaccine reduced the rate of IM but not virus infection. However, the researchers concluded it was not certain that a vaccine could induce immunity that protects from infection and could not determine that it could prevent EBV-associated malignancies. It also had no efficacy in preventing asymptomatic EBV infection. The authors concluded that the data supports the feasibility of using an EBV vaccine to prevent IM, but that more research needs to be done to come up with a single vaccine that is both safe and effective for other EBV-related conditions [22,29]. This study also referenced a possible vaccine that induces EBV-specific T-cell responses and could possibly be used for treatment of multiple sclerosis, provided it could be shown to be safe. A lengthy review of all of vaccine trials is beyond the scope of this review. For an extensive discussion on the history of EBV vaccine attempts, one can read a review published in *Clinical & Translational Immunology*, authored by Jeffrey Cohen [22].

### Dendritic cell therapy and anti-viral drugs

Getting deep into the mechanisms by which Dendritic Cell (DC) therapy works is beyond the scope of this review, but in general, DC therapy appears to elicit strong and long-lived antigen-specific T-cell immunity. Several cancer clinics are successfully using dendritic

cell therapies for cancer treatment. Interestingly, the therapy may be working in part due to its immune response to the EBV-infected cells. The DCs seem to sense the EBV-infected cells upon primary infection. These cells are thought to inhibit the EBV infection and initiate an adaptive immune response [30]. Current active immunotherapy trials have shown durable tumor regressions in patients [31]. Clinical trials have produced mixed results on DC therapy for various reasons, including that the majority of patients in these trials were last-stage metastatic patients that were previously treated with chemotherapy drugs. However, some smaller more recent trials were rather successful. One trial involved renal cell carcinoma [32] and another acute myeloid leukemia [33]. New trials are currently underway which have the potential to move DC therapy forward in the field of personalized medicine. Side effects of dendritic cell therapy may include flu-like symptoms like fever, rigors, tiredness as well as swelling and itching at the injection site. These usually go away by themselves quickly and rarely need treatment.

Other considerations for eradicating EBV being contemplated include targeting EBV-infected B cells with immunoglobulins and antiviral drugs. So far, little has been put to use as results have been varied. One report mentioned that Rituximab (an anti CD20 drug) has been somewhat successful, but can inadvertently deplete noninfected healthy B cells, as the expression of CD20 is not exclusive to EBV-infected malignant B cells. Treatment with rituximab has also been associated with an increased risk for opportunistic infections. An additional issue with rituximab is that it can interfere with lymphoma therapies, potentially rendering those treatments ineffective [34]. Another review determined that while numerous agents have been tried for the treatment of EBV, antiviral therapy is generally ineffective for this disease. This determination comes despite anecdotal evidence suggesting that these therapies (acyclovir, ganciclovir, vidarabine) might be effective. The researchers also concluded that immunoglobulin therapy has also been unsuccessful [35]. Notably, immunoglobulins and antiviral drugs come with a host of significant side effects, such as vomiting, dizziness, diarrhea, muscle or joint aches, visual changes, fluid retention, confusion, hair loss, and others.

However, while many drug therapies have proven to be ineffective, many natural substances have shown strong antiviral activity with little or no collateral damage to the host. Awareness of natural solutions by the clinician is also imperative to care for patients who remain averse to vaccines or drug therapies. While we do not yet have clinical trials to prove their efficacy against EBV, many natural substances are for the most part harmless to the human body and deserve further investigation.

## Natural Solutions

Given that persistent infection of EBV is a hallmark of oncogenic and otherwise detrimental pathogens, there is a window of opportunity for prevention by treating the pathogen before malignant progression of cancer begins, as well as initiation and progression of other chronic diseases and conditions. This author believes that attention must be given to non-toxic natural substances that could be helpful in deactivating EBV. Although not all natural compounds have been shown effective in clinical trials, this may be due to lack of funding for non-patentable items. Theoretical understanding of natural substances may suggest they are worthy of consideration.

This section offers a few examples of natural compounds that have antiviral and apoptotic therapeutic properties and which offer no harm to healthy cells and which do not come with significant side effects. While there are many natural anti-viral substances, this author has highlighted a few for consideration and believes that natural solutions can be effective in targeting EBV without the collateral damage of drug therapies. In lieu of a safe and effective vaccine or other pharmaceutical intervention, natural medicines may be helpful.

## Vitamin C

Studies have acknowledged the efficacy of high dose vitamin C supplementation involving multiple biochemical processes which aid in positive autoimmune response, inhibiting favorable conditions for viral replication. Vitamin C has been shown to inhibit cell growth and induce cell death (apoptosis) in a variety of cancers. Its antioxidant properties target the oxidant stresses of viral infection and work to detoxify and neutralize the reactive oxygen produced through the infection. Vitamin C also works to stimulate the body's production of anti-viral cytokines and interferon that boost the immune response to viruses and inhibit their cell growth [36]. One study found that intravenous vitamin C in the ranges from 7.5g to 50g vitamin C demonstrated a positive effect on disease duration and reduction in viral antibody levels. The study evaluated over 200 patients who had clinically elevated levels of EBV, some with chronic fatigue syndrome and some with IM and others with EBV infection. In other words, the researchers found that patients with high levels of vitamin C tended to have lower levels of antigens in the acute state of disease. They further concluded that the reduction in EBV antibody levels during IVC therapy hinders viral infection and replication. In addition, a relation was also found between vitamin D levels and EBV with lower levels of EBV early antigen for higher levels of vitamin D [37].

IVC has been used for decades and has been found to be safe with minimal to no side effects. There are a few medical conditions that prevent the use of IVC, including certain heart and kidney conditions, as well as high iron levels, so it is important for patients to consult their doctor prior to use. Patients with a rare inherited disorder called G-6-PD deficiency should not be given high doses of vitamin C due to the risk of hemolysis (a condition in which red blood cells are destroyed).

## Vitamin D

Mounting research involving vitamin D indicates that this hormone plays a key role in optimizing the function of the immune system. Reduced sunlight or inadequate D3 supplementation could aggravate cytotoxic T-cell problems thus inhibiting control of EBV. As discussed earlier in this review, vitamin D appears to stimulate the production of certain blood cells that play a key role in immune function and the expression of several genes that may be involved in infection-fighting pathways. A 2017 study determined that high-dose oral vitamin D3 supplementation can improve immune responses against EBV [38]. Numerous studies link low vitamin D levels and EBV exposure to incidence of MS [39,40]. A study conducted at the University of Oxford suggests that maintaining adequate levels of vitamin D may have a protective effect and lower the risk of developing MS. A study published in JAMA in 2006 reported that high circulating levels of vitamin D are associated with a lower risk of MS [41]. Other studies have found that vitamin D may lessen the frequency and severity of MS symptoms. Data from a study published in Molecular

Aspects of Medicine supports the consideration of vitamin D for the treatment of chronic EBV infection. The researchers concluded that NKT (Natural Killer T) cells depend on vitamin D for development and are up regulated by D3, but that other factors such as immunity of the host as well as the expression of the VDR may come into play, so further research was recommended [42]. However, this would imply that vitamin D should be kept at optimal levels as activation of the vitamin D receptor helps destroy cancer cells and may affect numerous other disease conditions. Vitamin D also has regulatory effects on cell cycle progression and apoptosis [43]. Collectively these studies may a good argument that vitamin D should be considered for EBV-affected patients. Although uncommon, excessive amounts of vitamin D in the body can lead to toxicity.

### Licorice Root and Quercetin

Licorice is the root of *Glycyrrhiza uralensis* or *G. glabra* that has traditionally cultivated in eastern part of Asia. More than 20 triterpenoids and nearly 300 flavonoids have been isolated from licorice. It is reported to have anti-viral, anti-microbial, anti-inflammatory, anti-atopic, hepatoprotective, anti-neurodegenerative, anti-tumor, anti-diabetic effects and so forth [44]. Quercetin is produced from licorice (it is also found in grapes, onions, apples, red wine, and berries). Importantly, licorice and its constituent quercetin could be an effective antiviral and apoptotic agent against EBV infection given its vast antiviral properties [45-47]. It has also been found to inhibit various types of cancer (breast, leukemia, colon, ovary, endometrial, gastric and non-small-cell lung cancers). It inhibits the production of leukotrienes and prostaglandins, inhibits lymphocytes, and suppresses macrophage phagocytosis. Quercetin helps to activate tumor suppressor genes p53 and p21, which deactivate in cancerous states. Quercetin also inhibits tyrosine kinase, one of the major enzymes associated with cancer. Licorice root should not be taken in high dose or for excessive amounts of time or side effects such as increased blood pressure and reduced potassium levels can occur.

### Olive Leaf Extract, Coconut and Other Natural Substances

Research shows that some other natural substances, such as olive leaf extract, are potent antiviral agents. For example, in a study published in Scientia Pharmaceutica, the authors explained the pharmacological effects of olive leaf, which include antiviral, anti-inflammatory, antimicrobial, and anticancer effects [48]. Studies have shown that phenolic compound oleuropein in olive leaf extract has potent antiviral activities against herpes, mononucleosis, and other viruses [48]. Monolaurin, a lipid extract from coconut, has powerful antiviral, antibacterial, and antipathogenic activity [49]. It may work against the virus by disintegrating the protective lipid envelope surrounding the virus, facilitating the death of EBV cells [50].

A notable 2005 study presented in Evidence-Based Complementary and Alternative medicine found that various probiotics, fruits, vegetables, spices, and apoptogenic plants help to modulate the immune system and help prevent chronic diseases [51]. Some examples are astragalus, bee propolis, lysine, and zinc. These substances have been found to inhibit EBV by many holistic doctors, but more research and trials need to be done to confirm efficacy.

### Testing for EBV

The connection between EBV and various conditions can easily be missed by medical doctors as many symptoms overlap. The pleomorphic nature of EBV can also mislead the clinician. EBV can switch from latent to lytic at any time, often triggered by environmental toxin exposure. Testing for active infection is important, with a full range of markers tested. These include CVA IgM, VCA IgG, EBNA IgG, EA IgG and EBNA IgM. EA IgG is the most important and necessary marker for current or chronic reactivation status. EBNA IgM is rarely tested but can indicate current reactivation.

### Conclusion

What started out as a causal connection between EBV and lymphoma now has far broader implications. EBV is etiologically and unmistakably linked with the development of numerous disease conditions. Awareness at the clinician level is necessary, and from what has been presented here natural solutions may be a favorable path for deactivating the virus. Clearly more research needs to be done but given the well-studied and documented correlation between this virus and oncogenetic events as well as incidence of other diseases it is imperative that we not wait for a vaccine to implement preventive and life-saving interventions with patients. Further research may be needed to facilitate the transfer of this information from scientists to medical personnel.

### References

1. <https://www.cancer.org/cancer/hodgkin-lymphoma/causes-risks-prevention/risk-factors.html>
2. Young LS, Dawson CW (2014) Epstein-Barr virus and nasopharyngeal carcinoma. Chin J Cancer 33: 581-590.
3. Hu H, Luo ML, Desmedt C, Nabavi S, Yadegarynia S, et al. (2016) Epstein-Barr virus infection of mammary epithelial cells promotes malignant transformation. Ebiomedicine 9: 148-160.
4. ScienceDaily (2012) Two viruses link to prostate cancer: High-risk human papilloma virus found with Epstein Barr virus. University of New South Wales, ScienceDaily, Rockville, USA.
5. Khasraghi SM, Ghane M, Ameli M (2014) Detection of Epstein-Barr virus in colorectal cancer and Polyp by using PCR technique. Journal of Paramedical Sciences 5: 96-101.
6. Janegova A, Janega P, Rychly B, Kuracinova K, Babal P (2015) The role of Epstein-Barr virus infection in the development of autoimmune thyroid diseases. Endokrynol Pol 66: 132-136.
7. [http://www.whirledfoundation.org/wp-content/uploads/2015/10/0212\\_Viral-Theory-For-Menieres-Disease.pdf](http://www.whirledfoundation.org/wp-content/uploads/2015/10/0212_Viral-Theory-For-Menieres-Disease.pdf)
8. Calenoff E, Zhao JC, Derlacki EL, Harrison WH, Selmezi K, et al. (1995) Patients with Meniere's disease possess IgE reacting with herpes family viruses. Arch Otolaryngol Head Neck Surg 121: 861-864.
9. [https://www.sinuswars.com/tinnitus/Bacteria\\_Viral\\_causes\\_Meniere's\\_disease.asp](https://www.sinuswars.com/tinnitus/Bacteria_Viral_causes_Meniere's_disease.asp)
10. <http://menieresjourney.blogspot.com/p/menieres-herpes.html>
11. <https://www.envita.com/lyme-disease/keys-to-uprooting-chronic-fatigue-syndrome-epstein-barr-virus-and-infectious-mononucleosis-lyme-disease-complex>
12. Jun HS, Yoon JW (2004) A new look at viruses in type 1 diabetes. ILAR Journal 45: 349-374.

13. Morales-Sánchez A, Fuentes-Pananá EM (2014) Human viruses and cancer. *Viruses* 6: 4047-4079.
14. Pender MP (2012) CD8+ t-cell deficiency, Epstein-Barr virus infection, vitamin D deficiency, and steps to autoimmunity: A unifying hypothesis. *Autoimmune Diseases* 16.
15. White JH (2008) Vitamin D signaling, infectious diseases, and regulation of innate immunity. *American Society for Microbiology* 76: 3837-3843.
16. Lin R (2016) Crosstalk between vitamin D metabolism, VDR signalling, and innate immunity. *BioMed Research International* 5.
17. Cantorna MT (2011) Why do T cells express the vitamin D receptor? *Ann N Y Acad Sci* 1217: 77-82.
18. NIH (2018) Epstein-Barr virus and autoimmune diseases. NIH, Maryland, USA.
19. Osatoa T, Imai S (1996) Epstein-Barr virus and gastric carcinoma. *Seminars in Cancer Biology* 7: 175-182.
20. Horwitz MS (2013) Epstein-Barr virus and autoimmunity. *Future Virology* 8: 173-182.
21. Draborg AH, Duus K, Houen G (2013) Epstein-Barr virus in systemic autoimmune diseases. *Clin Dev Immunol* 2013: 535738.
22. Cohen JI (2015) Epstein-Barr virus vaccines. *Clinical & Translational Immunology* 4: 32.
23. Yahia ZA, Adam AAM, Elgizouli M, Hussein A, Masri MA, et al. (2014) Epstein Barr virus: A prime candidate of breast cancer aetiology in Sudanese patients. *Infect Agent Cancer* 9: 9.
24. Dittfeld A, Gwizdek K, Michalski M, Wojnicz R (2016) A possible link between the Epstein-Barr virus infection and autoimmune thyroid disorders. *Cent Eur J Immunol* 41: 297-301.
25. Toussiroit E, Roudier J (2008) Epstein-Barr virus in autoimmune diseases. *Best Pract Res Clin Rheumatol* 22: 883-896.
26. <https://www.sciencedaily.com/releases/2017/02/170213131346.htm>
27. <https://medicalxpress.com/news/2018-04-epstein-barr-virus-linked-diseases.html>
28. Crawford DH (2001) Biology and disease associations of Epstein-Barr virus. *The Royal Society* 356: 461-473.
29. Sokal EM, Hoppenbrouwers K, Vandermeulen C, Moutschen M, Léonard P, et al. (2007) Recombinant gp350 vaccine for infectious mononucleosis: A phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of an Epstein-Barr virus vaccine in healthy young adults. *J Infect Dis* 196: 1749-1753.
30. Christian M (2014) Dendritic cells during Epstein-Barr virus infection. *Front Microbiol* 5: 308.
31. Palucka K, Ueno H, Fay J, Banchereau J (2010) Dendritic cells and immunity against cancer. *J Intern Med* 269: 64-73.
32. Kugler A, Stuhler G, Walden P, Zöller G, Zobywalski A, et al. (2000) Regression of human metastatic renal cell carcinoma after vaccination with tumor cell-dendritic cell hybrids. *Nature Medicine* 6: 332-336.
33. Tendeloo VFV, de Velde AV, Driessche AV, Cools N, Anguille S, et al. (2010) Induction of complete and molecular remissions in acute myeloid leukemia by Wilms' tumor 1 antigen-targeted dendritic cell vaccination. *PNAS* 107: 13824-13829.
34. Lai J, Tan WJ, Too CT, Choo JAL, Wong LH (2016) Targeting Epstein-Barr virus-transformed B lymphoblastoid cells using antibodies with T-cell receptor-like specificities. *Blood* 128: 1396-1407.
35. Cohen JI (2009) Optimal treatment for chronic active Epstein-Barr virus disease. *Pediatr Transplant* 13: 393-396.
36. Carr AC, Maggini S (2017) Vitamin C and immune function. *Nutrients* 9: 1211.
37. Mikirova NA, Hunninghake R (2014) Effect of high dose vitamin C on Epstein-Barr viral infection. *Med Sci Monit* 20: 725-732.
38. Røsjo E, Lossius A, Abdelmagid N, Lindstrøm JC, Kampman MT, et al. (2017) Effect of high-dose vitamin D<sub>3</sub> supplementation on antibody responses against Epstein-Barr virus in relapsing-remitting multiple sclerosis. *Mult Scler* 23: 395-402.
39. Anderson P (2012) Low Vitamin D, Epstein-Barr, Linked to Later MS. *Medscape*, New York, USA.
40. Carlson NG, Rose JW (2013) Vitamin D as a clinical biomarker in multiple sclerosis. *Expert Opin Med Diagn* 7: 231-242.
41. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A (2006) Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 296: 2832-2838.
42. Cantorna MT, Yu S, Bruce D (2008) The paradoxical effects of vitamin D on Type 1 mediated immunity. *Mol Aspects Med* 29: 369-375.
43. Tabasi N, Rastin M, Mahmoudi M, Ghoryani M, Mirfeizi Z, et al. (2015) Influence of vitamin D on cell cycle, apoptosis, and some apoptosis related molecules in systemic lupus erythematosus. *Iran J Basic Med Sci* 18: 1107-1111.
44. Wang L, Yang R, Yuan B, Liu Y, Liu C (2015) The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. *Acta Pharm Sin* 5: 310-315.
45. Brooks L, Yao QY, Rickinson AB, Young LS (1992) Epstein-Barr virus latent gene transcription in nasopharyngeal carcinoma cells: Coexpression of EBNA1, LMP1, and LMP2 transcripts. *J Virol* 66: 2689-2697.
46. Lee M, Son M, Ryu E, Shin YS, Kim JG, et al. (2015) Quercetin-induced apoptosis prevents EBV infection. *Oncotarget* 6: 12603-12624.
47. Cheel J, Onofre G, Vokurkova D, Tůmová L, Neugebauerová J (2010) Licorice infusion: Chemical profile and effects on the activation and the cell cycle progression of human lymphocytes. *Pharmacogn* 6: 26-33.
48. Omar SH (2010) Oleuropein in olive and its pharmacological effects. *Sci Pharm* 78: 133-154.
49. Lieberman S, Enig MG, Preuss G (2006) A review of monolaurin and lauric acid: Natural virucidal and bactericidal agents. *Alternative and Complementary Therapies* 12.
50. Isaacs CE, Kim KS, Thormar H (1994) Inactivation of enveloped viruses in human bodily fluids by purified lipids. *Ann N Y Acad Sci* 724: 457-464.
51. Haddad PS, Azar GA, Groom S, Boivin M (2005) Natural health products, modulation of immune function and prevention of chronic diseases. *Evid Based Complement Alternat Med* 2: 513-520.