**Vitamin D and Erythematous Systemic Lupus**

Erythematous Systemic Lupus, which I’ll refer to simply as “Lupus” from here on, is a systemic autoimmune disease with genetic, immunological, hormonal and environmental causes (1). One of the environmental causes which was investigated over the years is Vitamin D, (which is formed in the human body in the aftermath of the body’s exposure to sunlight and to Ultraviolet radiation (UV).

The purpose of this study is to investigate the findings of the last few years, 2013-1014, with regard to the connection between a Vitamin D deficiency and the outbreak of Lupus, as well as the extent of its severity and its expression, and also to test the therapeutic possibilities which are implied by this connection.

**Vitamin D**

Heliotherapy, a treatment using sunlight, has been in usage as far back as the days of Egyptian domination, as well as in ancient Greece and Rome. Those ancient peoples used the sun’s light, which they regarded as a “Divine” source, to treat various medical problems. Similarly, in the ancient Hindu, Assyrian and Inca culture, there are reports of the same kind of activity.

In modern times, Dr. Niels Riverg Pinsenxxx was the first to use the light’s radiation to treat infectious dermatological diseases and especially , lupus vulgaris. His research won him the Nobel Prize for medicine and physiology in 1903. Dr. Pinsenxxx, like many others, saw sunlight radiation as an ameliorating cause especially as far as dermatological pathologies were concerned (2). In the beginning of the last century the relationship between a lack of exposure to sunlight and Ricket’s, a bone disease , which affects children, and it’s influence on the calcium and Phosphorous interfaces in the body, was revealed.

Reasearch from the 1980’s has demonstrated molecular changes in the immune systems of healthy people following the use of Solarium (3). These studies and others lay the foundations for the modern research on the effect of Vitamin D on the immune system in general and on immunomodulation in particular.

The role of Vitamin D in the regulation of the Calcium and Phosphorous interfaces , has been extensively researched and in the last few years evidence has been increasingly found of the involvement of Vitamin D in a variety of processes in the Immune System (4,5). Thus, for instance Vitamin D receptors were discovered on cells within the Immune System, such as, Macrophages, Dendrites, T-cells and B-cells (4,6).

Life in the modern world has transferred the main activity of human beings away from sunlight and in this way exposed them to a variety of autoimmune diseases, which are estimated to be on the constant rise. Among the diseases which were found to be connected to a Vitamin D deficiency are, Multiple Sclerosis, Type One Diabetes, Infectious Intestinal diseases, Rheumatoid Arthritis and more (4,7). As far as Lupus is concerned, the situation is somewhat more complicated since, although sunlight and Ultraviolet radiation have positive immunomodulatorial xxx influence and are supposed to ameliorate the disease, yet it has been proven that the symptoms of those afflicted with Lupus are worsened by the radiation. A review which was recently published on the subject supports the relationship between Ultraviolet radiation and the worsening of the dermatological symptoms which are prevalent in Lupus, but has not been able to establish the hypothesis that radiation is in fact a source of hazard in the eruption of the disease.

**A Vitamin D deficiency:**

There lacks a consensus within the medical literature as regards the definition of a Vitamin D deficiency. An accepted definition for the deficiency is a value in 25-Hydrocyvitamin D serum (25 (OH)D is the method by which the vitamin is measured in the blood) of under 30-40 ng/mL, since beneath this level a Para-Thyroidxxx activity begins which affects harm to the bones (9,10), and also there’s an increase in the risk of fatal diseases, Blood vessels diseases and autoimmune diseases (11). In some of the articles is found a subdivision into “partial deficiency” (21-29 ng/mL) and “full deficiency” (under 20ng/mL) (10,12-14) and some define an even lower level (9,15). An optimal level of the functioning of the Immune System within the appropriate range of a concentration of Vitamin D in the serum, has yet to be defined (10). A Vitamin D deficiency is more prevalent among those afflicted with Lupus than among healthy subjects (16,17); more prevalent in women than in men, regardless of the presence or lack thereof of the disease (15); and in Afro-Americans more than in white subjects (14,18-20). Similar findings were demonstrated in youths and young adults who were diagnosed with Juvenile onset systemic lupus erythematosus (21) (JSLE).

Several explanations have been offered for the possible differences in Vitamin D levels between healthy and afflicted individuals: Those afflicted with Lupus had been instructed to avoid sunlight due to photosensitivity and this contributed to their Vitamin D deficiency. Another explanation can be found in the harm caused to the kidneys of those afflicted with Lupus, which defect damages the activation of the vitamin. Similarly, the medicinal treatment of the disease, such as for example, the use of Steroids, harms the metabolism of Vitamin D (6,14,22).

**Polymorphism in the VDR-receptor**

The Vitamin D, VDR-receptor, is a receptor for a nuclear hormone. The gene for this receptor is highly polymorphic and that can affect its functioning and as a byproduct of that, affect the levels of active Vitamin D in the blood (10). Under such circumstances, genetic difference In the receptor can possibly explain Vitamin D deficiencies in various populations. There are a number of SNP’s (Single Nucleotide Polymorphism) known to this receptor, four of which have been investigated extensively. Namely, Taql, Bsml, Apal and Fokl.

Three meta-analyses which were published during the last two years in various magazines, examined the relation between the disease and genetic polymorphism in an investigation of ethnic origin. In all three the results of those investigations were studied and one of those analyses included two additional researches which will be discussed later.

In the first two meta-analyses which were published in 2013, a relation between a B-allele of Bsml and the eruption of the disease in the general population and also and especially among Asians, was found . In one of them, Mao et al. a relation was found between the FF genotype of Fokl and an increase in the risk of becoming afflicted among Asians (23), While in the other meta-analysis, Xiong et al. a relation was found to the genotypes, FF and Ff, in the general population and also among Asians (24). The third Meta-analysis, Zhou et al. which was published in 2014, included two additional studies of Lupus among Polish individuals as well as among Egyptian individuals. In the Polish research a difference in the segmentation of the different genotypes of BsmI between individuals afflicted with Lupus and healthy individuals and a connection between a specific genotype and the clinical expression of the disease was not found, but a correlation was found between the bb genotype and high levels of self-antibodies of the ANA type (25). The Egyptian study found a connection between the disease and the genotype AA of Apal, Allele B and genotypes BB and Bb of Bsml and the allele F and the genotype FF of Fokl and likewise as far as the philotypes xxx aBF and ABF. Also, a connection was found between genotypes AA, BB and FF and kidney involvement and high disease activity and lower levels of Vitamin D were seen in the FF carriers of Fokl as compared with ff (26). In the statistical analysis of the latter Meta-analysis, a connection was found between the disease and the aa genotype of Apal, allele B and genotype bb of BsmI and the allele F and genotype ff of FokI in the general population. In Asians , allele B and genotype BB and Bb of BsmI , and allele f and genotype ff of FokI (and not FF as in the first two meta-analyses) were found to be risk factors for the disease and the same is true in Africans, with whom an additional connection was found to the allele A and the genotypes Aa and aa in ApaI. In whites, a connection was not found between the risk to becoming ill with the disease and genetic polymorphism (27). The differences between the meta-analyses are not clear, therefore, since the studies which differentiate between them do not relate at all to the Asian population.

Silva et al. expanded the search for the SNP’s relevant to the disease and tested five Tag SNP’s in a gene for VDR besides the ones mentioned above, in a way which covers the majority of the genetic range. Tag SNP is a specific nucleotide which represents a genomic segment which has a high unequal linkage, or in other words contains changes in SNP which tend to appear together. Researchers failed to find a connection between specific Tag SNP’s and the actual presence of the disease, but they did find a connection to specific clinical expressions of the same disease: Dermatological changes, joint disease, changes in immunization and the presence of anti-dsDNA antibodies ( In SNP’s, rs11168268, rs3890733, rs3890733, rs2248098, rs4760648 respectively) (28).

**Vitamin D deficiency, cells and mediators within the Immune System**

The role of neutrophil granulocytes in the pathogenesis of the disease is a relatively new realm of study. Neutrophil granulocytes are a part of the congenital immune system and their role in Lupus, a disease known to be an acquired immune system disease, is not self- evident. Neutrophil granulocytes defend against external pollutants in a variety of ways and the newest among them to be discovered is by way of creating neutrophil extracellular traps (NETs). NET’s are structures which resemble nets made of chromatin and various proteins, which neutralize pollutants and in the process cause NETosis, a planned death of the neutrophil granulocytes themselves (29,30). The regulation of the formation and dismantling of the NET’s is very important, since any disturbance to the process is likely to cause damage to the tissue itself and bring about the exposure of self-antigens. Previous studies, in vitro have found an imbalance between the formation and dismantling of the NET’s in neutrophil granulocytes which were retrieved from individuals afflicted with Lupus (31,32). These researches as well as others offer a relation between the exposure of antigens in the process of NETosis, and creating antibodies against nuclear particles and against the chromatin itself (anti-ds-DNA), which particles are known as a part of the pathogenesis of the disease (30).

Due to the known influence of Vitamin D on the regulation of the Immune System, a group of researchers chose to examine that influence on the NETosis process. In a limited molecular research, researchers isolated neutrophil granulocytes out of five women, afflicted with Lupus, and divided them into four therapeutic groups, which were soaked for a period of 24 hours, in different dosages of Vitamin D (0, test xxx, 1nM, 10nM, 100nM). In each therapy group a significant decrease was viewed in the secretion of NE (neutrophil elastase) which constitutes an indicator to NETosis, and also a significant decrease in the early apoptosis of andotalxxx cells in the therapy group at a dosage of no more than 10nM, and not in the other groups. The damage to the andontalxxx cells has been related to mediators which are secreted in the process of NETosis and cause damage to adjacent tissue (33).

Dendrite cells are related to the regulation of the immune system and changes in their homeostasis are also related to the pathogenesis of the disease. Research which was done in persons afflicted with Lupus showed that Alpha-interferon (IFN-Alpha xxx) influences the cellular differentiation of monocytes into dendrite cells, which exhibit self-antigens to the immune system and participate in the autoimmune reaction. Dendrite cells can activate Naïve T-cells and to stimulate B-cells into growth and differentiation (34,35).

In a research in which monocytes and lymphocytes of Lupus afflicted individuals were soaked in Vitamin D, in a protocol similar to the experiment above , it was found that the treatment, especially at the 10nM dosage, lowered the ripening of dendrite cells (which was measured with the expression, CD40, CD86, HLA-DR) and brought about a decrease in the secretion of the mediator IL-12p70 of the infection from those same cells. Similarly, a decrease was viewed of the percentage of Th17 cells out of the T-cells, which are related to autoimmune diseases(36) and a decrease in their IL-17A secretion (37).

Dendrite cells encourage an immune tolerance, among other things, via their influence on T-regulators (Treg-regulatory) (38). T-cells in general and Treg cells in particular, constitute an important part of the pathogenesis of the disease (39). Treg cells are cells of the type, CD4+, which express a CD25+ marker, and they have an important role in regulating the immune system. Previous researches demonstrated a quantitative increase in Treg cells in individuals with an active disease (40) as well as changes in their activity (39) and therefore an increase in their quantity and an improvement of their functioning constitute a treatment goal (41). To that end we will test, among other things, a granting of Vitamin D supplements (42).

In a research conducted in 2014, researchers demonstrated a decrease in the expression of factors related to energy with T-cells of afflicted individuals, as compared with healthy individuals. Similarly, it was found that exposure of T-cells of afflicted subjects to Vitamin D treatment caused an increase in the expression of Treg-cells markers and to the raising of their numbers. Similar findings and even more significant were demonstrated in an exposure to רפמיצין xxx

The influence of Treg cells on their environment is made possible, among other things, by their ability to wander. One of the factors which enable their wandering is a chemokine receptor of the type, CCR4 (C-C chemokine receptor type 4) which is expressed by them. In an Indonesian research, researchers asked to test the influence of Vitamin D of the expression CCR4 and on the ability of Treg –cells to wander. In this research a positive coordinator was found between levels of Vitamin D and the ability of the cells to travel, with no relation to the status of the disease, but a difference between the CCR4 expression in Treg cells in afflicted individuals as compared to healthy individuals , was not found. Therefore, researchers concluded that the ability of cells to wander within the context of the disease is not mediated by this receptor (44).

**A Vitamin D deficiency and the disease symptoms:**

The SLEDAI scale (Systemic Lupus Erythematosus Disease Activity Index) was formed in 1992, in order to create uniformity in the evaluation of the activity of Lupus disease within medical research. The scale includes 24 variables, of which 16 are clinical and 8 are laboratory and the involvement of each organ in the disease receives a different value in the calculation of the final score. The evaluation relates to variables which are present at the time of the examination or else during the ten days which preceded it. The score according to the scale is between 0-105 and a score of 6 and above indicates an active disease (45). The SELENA-SLEDAI scale (SELENA- safety of Estrogen in Lupus Erythematosus National Assessment ) is an adjusted calculation of the former and it relates also to the influence of Estrogen in a number of variables, without change in the calculating system (46).

Schoindre et al’s research examined the relation between levels of 25(OH)D and the activity of the disease and its eruption accordinf to the SELENA-SLEDAI scale. Researchers followed 170 afflicted subjects, treated with הידרוקסיכלורוקווין for a period of seven months and found a coordinator between low levels of the vitamin and a higher score on the SELENA- SLEDAI scale but could not show a connection to the risk of eruptions, during the six months following the examination (15). The research credited to Lertratanakul et al. demonstrated the complementary conclusion, that high levels of the vitamin are related to a lower score on that scale (47). Similar findings were also predicted in researches conducted in India (48) in Egypt (26) and in a dark skinned population in Jamaica, in which there’s a significant Vitamin D deficiency (13) , (the activity of the disease in this research was measured using the BILAG scale (British Isles Lupus Assessment Group)) (49) and in youths (21). Support for these findings was found in the literature reviews which were done on the subject recently (6,14 ,50).

On the other hand, in other researches, which were more limited as to their range, researchers had a hard time showing the relation between a Vitamin D deficiency and the activity of the disease, whether it was measured on a SLEDAI scale (12, 51), or in the SLEDAI-2K (52) and MEX-SLEDAI scales(22), both of which are modifications of the SLEDAI scale (53,54). In addition a connection was not found between the levels of the vitamin and eruptions, even when they were evaluated according to the self reported flares of the afflicted (16).

In a literature review on the subject which was done in 2014, and which included also a meta- analysis of 35 articles from the last two decades, researches wanted to isolate the variables which are involved in the relation between levels of Vitamin D and the expressions of the disease. The variables which were found to be the most significant were medicines (

הידרוקסיכלורוקיווין, steroids and Vittamin D supplements), BMI, (Body mass index) kidney function and proteinuria (51).

**Heart and Blood Vessels diseases and the metabolic syndrome:**

Individuals sick with rheumatic diseases in general, and Lupus in particular are found to be at high risk for the acquisition of heart and blood vessels diseases. The reasons for this have to do with the infection itself, with disturbances in the immune system as well as treatments of the disease (55, 56). It is customary to separate the risk factors into three groups: “Traditional” risk factors (such as, smoking , obesity, high blood pressure, דיסליפידמיה, Insulin resistance, Diabetes and the metabolic syndrome); risk factors related to the disease itself (such as, self antibodies, infectious proteins, פרופיל ציטוקונים , an inbalance in Th7/Treg, a deficiency in C2 and interferon of Type 1); and risk factors related to treatment of the disease (as for example the use of Prednisone ) (57-59).

During the last few years the possibility was examined that this relation is mediated, at least in part, by a Vitamin D deficiency (which is common in Lupus afflicted individuals, as said earlier), since heart and blood vessels diseases were related to a Vitamin D deficiency in the general population as well (5, 60). An international cohort study which included 890 subjects, supports this hypothesis. The research found an independent relation between levels of Vitamin D which were relatively low, and the risk of suffering excessive blood pressure and hyperlipidemia in Lupus afflicted individuals, but did not find a relation between Vitamin D levels and cardiovascular events, which is not mediated by these variables. That research suggests, therefore, that the relation between heart related events and a Vitamin D deficiency, is in fact mediated by “traditional” cardiovascular risk factors (47). A different research which tried to explain the connection between excessive blood pressure and Vitamin D, suggests that the relation is mediated, at least in part , by it’s influence of the Renin Angiotensin system(61). A literature review on the subject reached similar conclusions and found a connection between a Vitamin D deficiency and the risk factors mentioned above, as well as insulin resistance (50).

A research which compared women afflicted with Lupus and healthy women (none of which had Diabetes) showed an inverse connection between 25(OH)D levels and insulin resistance in Lupus afflicted individuals, with no relation to the BMI. This connection was not found in the healthy women, something which could suggest an interaction between the disease itself and insulin resistance and Vitamin D deficiency(17).

Out of the literature review which was done by Iaccarino et al., recommendations arise for the prevention of blood vessels diseases and heart diseases in persons afflicted with Lupus. Researchers recommend lowering the traditional risk factors by balancing Diabetes, balancing excessive blood pressure and in as much as needed, taking medicines: ACE hinderers, אסיפירין, הידרוקסיכלורוקיווין, and Statins. As far as treatment for Lupus, one should aspire to bringing patients to long term remissions, by using steroid-sparing medicines at minimum steroid dosage. In addition, it’s necessary to encourage use of Vitamin D supplements (59).

On the other hand, not all of the studies on the subject support a relation between Vitamin D and heart disease or blood vessels disease among those afflicted with Lupus. In a cohort research conducted by Kiani et al. for a period of two years, researchers attempted to test the relation between Vitamin D levels and below clinical level atherosclerosis , such as the calcification of the Common Carotid Artery (CAC—coronary artery calcium, measured via CT scan) and the thickness of the intima—media layer of that same artery (IMT—intima –media thickness evaluated by Doppler Ultrasound). 154 subjects (out of 200) completed the research, in which a connection was not found between the levels of Vitamin D and below clinical level measurements of atherosclerosis (18). An additional research from Korea, which compared 102 women afflicted with Lupus to healthy women, reached similar conclusions. Researchers used a measurement of the thickness of the intima-media and also tested for the presence of plaques as well as measured their size in the arteries . As expected, the atherosclerosis measurements were considerably high among Lupus afflicted subjects, but this research too failed to demonstrate a relation between a Vitamin D deficiency and these measurements (62).

It follows, therefore, that the relation between heart disease as well as blood vessels disease among Lupus afflicted individuals , is still controvertial. Despite this fact, it’s possible to see recommendations within the literature for the offering of Vitamin D supplements to these patients.

Kidney Involvement:

Souza et al. showed in their research a higher estimate of Hematuria among subjects afflicted with Lupus with low levels of Vitamin D, as compared to subjects (with Lupus) with appropriate levels of Vitamin D and as compared with healthy individuals, but a connection to other measurements of נפריטיס גלומרולרי , including levels of קראטנין (12) was not found. On the other hand, a research conducted within the Thai population , managed to show a connection between higher קראטנין levels to a 25(OH)D deficiency in those afflicted (22) and another research showed a relation between low level of Vitamin D and proteinuria and to the presence of cylindrical precipitation in urine(26).

**Vitamin D deficiency and ציטוקינים**

C-reactive Protein CRP

CRP is a plasmatic protein which is produced in the liver and is related to infectious processes and acts as a sign for them. In an infectious condition, it’s secretion rises as a response to Interleukin-6 (IL-6), it connects to certain elements on top of dead cells and bacteria and activates the משלים system. In recent years a connection between high levels of CRP and the risk of cardiovascular disease was found (63).

In a research that was published in 2014, Souza et al. showed that a Vitamin D deficiency in Lupus afflicted individuals is related to higher levels of the ציטוקין IL-6, but not to hs-CRP (high-sensitive C Reactive Protein) levels (12). However, in a variable analysis from longer cohort studies, at the first moment in time, researchers managed to show a relation between a Vitamin D deficiency to the basic levels of hsCRP, both in adults (18, 47) and in youths (64) , also in the deduction from epidemiological mediating variables. However, levels of Vitamin D in adults failed over the course of time to predict changes in hsCRP (18).

Interferon alpha IFN- alpha xxx

IFN-alphaxxx is a part of the type 1 interferon cytokine family, which regulates the activity of the immune system. IFN-alphaxxx is involved, especially in the reactions of the immune system against Viral pathogens and is secreted for the most part from dendrite cells of the type plasmacytoid DCs (pDCs) (65). In the last few years a new term was coined, IFN signature, for the definition of a group of genes with a particular expression, which is related to the expression of autoimmune diseases in general and of Lupus in particular (66).

The involvement of IFN-alpha xxx in the disease was demonstrated in the findings of several researches: in the families of persons afflicted with Lupus high levels of interferon were viewed; exogenous administering of IFN-alphaxxx caused a disease resembling Lupus in some of the patients; and also it was found that high levels of IFN-alphaxxx constitute a risk factor for the disease (67,68). A research conducted in India showed a clear correlation between 25 (OH)D levels to IFN-alphaxxx levels, in the plasma of Lupus afflicted subjects and a similar correlation to the expression of genes to IFN-alphaxxx. Researchers also demonstrated a positive correlation between interferon levels and the severity of the expression of the disease (48).

**A Vitamin D deficiency and סרולוגיים autoimmune markers**

Many self-antibodies which act against extra cellular particles as well as intra cellular particles, have been found. The specification of these antibodies to the disease is varied and their role in the pathogenesis of the disease as well as its expression is not sufficiently clear (69).

ANA (Antinuclear antibodies) is a group of self-antibodies which act against particles in the core of the cell. It is a wide group of antibodies which show up in a number of autoimmune diseases, including Lupus. In a cohort research study which included 121 female subjects, researchers showed that the higher the concentration of 25(OH) D was in the blood of the subjects, the lower the chance of a positive titratesxxx of ANA antibodies ( which has been defined as a concentration of 1:80 and above) (16).

Antibodies which act against double stranded-DNA (Anti double stranded-DNA- dsDNA) are regarded as very specific to the disease. They were found to be related to the משלים system in afflicted subjects as well as to the clinical expression of the disease (70). Research from the last few years showed a negative correlation between 25(OH) D levels and the presence of ds-DNA antibodies(26, 48, 52), while an interfering research, in which subjects were given Vitamin D supplements, couldn’t demonstrate a relation to the levels of self-antibodies of this type.

A sub-type of anti dsDNA antibodies, which was found in some of the subjects afflicted with Lupus and was regarded as very specific, is the anti-telomere antibody (69, 71). Telomeres are sequences of double stranded חוזרניים (repeated?) DNA (TTAGG=CCCTAA) n, which are found at the end of the chromosome and influence the life span of the cell, relative to their length and their ability to renew themselves. Previous studies have shown that in addition to the presence of these antibodies in Lupus afflicted individuals, their telomeres are shorter by comparison to healthy individuals (72). In a research conducted in Afro-American women it was found, as expected, that they had higher levels of anti- telomeres antibodies and shorter telomeres by comparison to healthy women, but in addition a positive correlation was found between levels of antibodies and the clinical expression of the disease and between shorter telomeres and a Vitamin D deficiency with no relation to the status of the disease (73).

A Vitamin D deficiency and the משלים system

A research from Saudi Arabia showed a connection between low levels of משלים, which constitute a marker for an active disease, and low levels of 25 (OH)D as well as a positive if not obvious correlation between the vitamin and a C4 particle of the משלים system, but couldn’t manage to show the same relation to the C3 particle (52).

Vitamin D supplements for Lupus afflicted subjects/ Vitamin D treatment

The assumption that there exists a relation between Vitamin D and Lupus which was present in some of the research studies, lead to attempts to examine its essence and its direction, via interfering studies which made use of Vitamin D supplements. The accepted dosages according to the literature are, 800, 2,000 and 4,000 IU units a day and some researches recommend to correlate the dosage with the basic levels of the vitamin of the subject as well as to individual risk factors (BMI, use of steroids and more) (6,10).

Petri et al. conducted a long cohort research with many participants, within the framework of which were given Vitamin D supplements to each subject whose levels of 25(OH)D were lower than 40ng/mL (50,000 units (IU) of D2 a week and 200 units of Calcium/D3 twice a day). Researchers showed an improvement in the proteinuria (which was measured in relation of protein to קראטנין at higher 25(OH) D levels, a finding which was viewed also in another research conducted on children (74). Similarly, a correlation was seen between measures of the activity of the disease (which were measured using the SELENA\_--SLEDAI scale and in accordance with a physical examination by a physician) and the change in 25(OH)D values. Note that this correlation was viewed only in diseased persons who had suffered from a Vitamin D deficiency at the start of the experiment. There was not found an influence on the activity of the disease once levels of the vitamin were raised to above 40ng/mL (20).

On the other hand, a literature review which was done recently, which examined articles on the subject from the last few years and which included also the above mentioned study, did not succeed in reaching unequivocal conclusions regarding the efficiency of the giving of Vitamin D supplements to afflicted individuals (10).

Today, there is no sweeping recommendation to give Vitamin D supplements to Lupus afflicted individuals, with the exception of patients treated with steroids, to whom it is recommended that they be given a dosage of 800-1,000 units per day (75).

**Miscellaneous**

In light of the significant findings which were discovered regarding the involvement of Vitamin D in Lupus, many researchers wished to find a connection between it and other variables relevant to the disease. A relation between a Vitamin D deficiency and sleep disturbances was found and tested (evaluated in accordance with questionnaires) which is not mediated by epidemiological variables or by the psychological condition of the diseased (76). The relation between Vitamin D and infecting with the Papilloma Virus (human papilloma virus HPV) was examined and was it was found that among women affected there was a higher rate of deficiency of this vitamin and a higher rate of infecting with the virus, but the relation between these two phenomena was not clearly seen (77).

**Summary**

A Vitamin D deficiency is more common among individuals afflicted with Lupus than among members of the general population, but a causal relation is yet to be determined. The possible explanations for this phenomenon are among others the avoidance of persons afflicted with Lupus of a direct exposure to sunlight, the involvement of kidneys in the disease, and the medicinal treatment of the disease. An additional possible explanation can be found in the genetic difference and in the VDR Vitamin D receptor.

It was found that Vitamin D has a moderating influence on the Immune System and on processes relating to the various cells within it. In this review we discussed its influence on the quantity as well as the activity of Neutrophil granulocytes , dendrites and T-cells. At the clinical level, it seems that a Vitamin D influences the activity of the disease as well as its hitting of the aimed for organs. On the other hand, interfering researches have not reached unequivocal conclusions with regard to the treatment of the disease, using Vitamin D supplements, except for the case of studies done on patients treated with steroids.

Determining the safety and efficiency of the use of Vitamin D as a way of treating the disease, and determining the precise dosage needed for this , requires conducting interfering studies of a wide range in addition to the ones already conducted. Such researches must emphasize and neutralize many variables such as, initial and final levels of the vitamin, the VDR genetics, exposure to sunlight and more, which variables could possibly interfere in this relation and change the results of the research studies.