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A REVIEW ON MARKETED IMPLANTS IN TREATMENT OF AUTOIMMUNE DISEASE

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Abstract

Given that the use of breast implants for both cosmetic and reconstructive purposes is growing in the United States, an evaluation of factors that may affect the outcome of breast implant surgery is needed. A systematic review was conducted to evaluate the question: Does a personal or family history of autoimmune disease affect outcomes in breast implant surgery? The literature search yielded 2425 records, but after removal of duplicates, abstract screening, and full-text assessment, only 2 studies met the inclusion criteria for the final review. Both studies provided level III evidence and the average Methodological Index for Non-Randomized Studies score was 16.5 (range, 15–18 of 24), indicating a fair level of evidence overall. This systematic review found no evidence to support that a diagnosis of an autoimmune disease and/or a family history of autoimmune diseases will lead to poor surgical outcomes in breast implant surgery. Further study is warranted.

INTRODUCTION [1]

Normally the function of immune system in our body is to recognize foreign elements and to destroy these before they could harm us either by humoral immune response (specific antibody formation) or cell mediated immune response by activation and clonal expansion of T cells. Thus the immune system defends the body against infections and certain other diseases by identifying, attacking, and destroying germs and other foreign substances. Sometimes the immune system makes a mistake and starts attacking the body's own tissues or organs. This is called autoimmunity. There are many autoimmune diseases one example being type 1 diabetes in which the Islets cells (produce Insulin) in the pancreas are destroyed by the immune system. An autoimmune disease is a case of mistaken identity; it is an abnormal condition in which the body reacts against constituents of its own tissues. The result may be simple hypersensitivity reaction and or autoimmune disease when the body begins attacking its own healthy tissues. We can say it is a case of mistaken identity resulting in failure of the immune system to differentiate between self and non self. About 5 % to 7 % of adults suffer from autoimmune diseases and two thirds of these are females. Somehow left handed people are more prone the reason for this is not known. This failure to differentiate between self and non self may result due to some extraneous environmental factors like some viral infections and exposure to some mutagenic agents; can be due to the breakdown and failure of immune regulation and due to some aberration in the genes. Whatever the reason the result is autoimmune disease which may involve a particular organ when it is called an organ specific disease (e.g. Addison's disease involving Adrenal glands) or it may involve particular cells/tissues all over the body when it is called non-organ specific or disseminated disease (e.g. Rheumatoid arthritis).

History

A very famous, Nobel laureate Paul Ehrlich (1854-1915) coined the term "Horror autotoxicus" to emphasize that body has innate aversion to immunological self-destruction. "Horror autotoxicus" literally means the horror of self-toxicity. However, as we now know, the immune system can upon occasion attack own body and result is autoimmune disorders. Scientists started talking about autoimmunity around 1900. By 1904 the antibody nature of the autohemolysin responsible for cold hemoglobinuria was described, and soon confirmed. However, the concept that autoimmunization caused cold hemoglobinuria was not yet clear and was not accepted. It was only during early 1960s that the concept of autoimmunization as cause of some diseases was accepted. The publication of a monograph on autoimmune disease in 1963, and surely by the consensus reached at a large international conference published as proceedings in 1965 lead to acceptance of the state of autoimmunity. The history of autoimmunity is far from over as autoimmunity is being incriminated in aetiopathogenesis of more and more disease conditions

" DEFINITION "

Autoimmunity refers to the body's development of intolerance of the antigens on its own cells i.e. there is an immune response to one's own tissue antigens. This type of body response results in a disease state characterized by a specific antibody or cell-mediated immune response against the body's own tissues (auto antigens). So, we can say that autoimmunity is the breakdown of mechanisms responsible for self tolerance and induction of an immune response against components of self. The immunological mechanism of the body is dependent on two major factors: (1) the inactivation and rejection of foreign substances and (2) the ability to differentiate between the body's own antigens ('self') and foreign ('non self'). It is not yet known exactly what causes the body to fail to recognize self proteins as its own and to react to them as if they were foreign resulting in autoimmunity and may be autoimmune diseases. Prominent examples include celiac disease, diabetes mellitus type 1 (IDDM), sarcoidosis, systemic lupus erythematosus and many others.

A. AUTOIMMUNE DISEASE STATES[1]

The autoimmune diseases can be divided into systemic, localized and haemolytic disorders, depending on tissue/cells affected and the clinico-pathologic features

a. Systemic autoimmune diseases[1]

These diseases are associated with auto antibodies to antigens which are not tissue specific. One example can be polymyositis, here the tissue involved are muscles, however the auto antibodies are found against the auto antigens which are often ubiquitous "t-RNA synthetases". Another example is rheumatoid arthritis (RA). There is symmetric poly arthritis with muscle wasting and may be associated with myositis, and vasculitis, etc. The specific marker (auto antibody) found in blood in these patients is Rheumatoid Factor (RF) which is usually 19 s IgM. RF is an antibody against Fc fragment of immunoglobulins. Other systemic autoimmune diseases are polyarteritis nodosa, systemic lupus erythematosus and Sjogren's syndrome as shown in the figure.

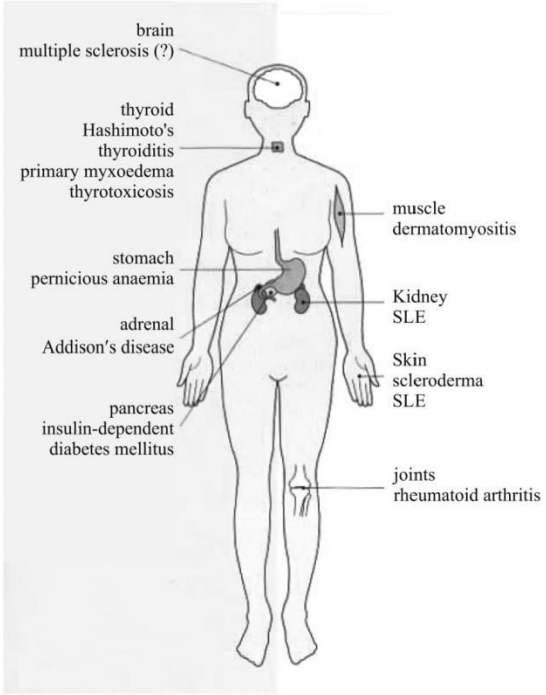

Fig. 1Two types of autoimmune disease

So, let us recap, in case of systemic autoimmune diseases the incriminating antigens and the autoimmunity are distributed in many tissues. The systemic diseases are:

i. Rheumatoid arthritis

ii. Systemic lupus erythematosus (SLE)

iii. Scleroderma

iv. Primary Sjogrens's syndrome

v. Polymyositis

I. Rheumatoid arthritis[2]:

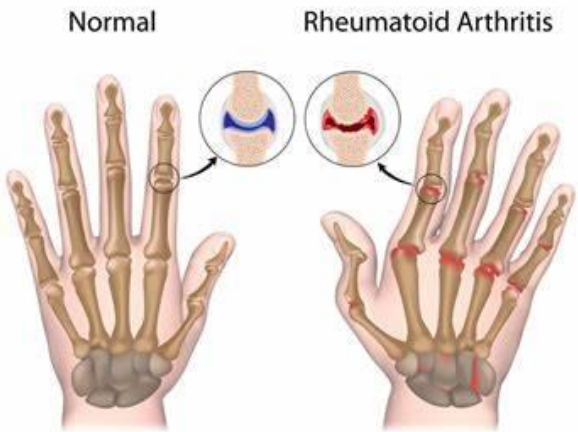

Fig.Rheumatoid arthritis

Rheumatic diseases were first recognized by Hippocrates in the fourth century B.C. In the first century A.D., the term 'rheuma' was first introduced to indicate a flow of pain through the joints of the body. The appearance and distribution of lesions in ancient skeletons suggest that rheumatoid arthritis (RA) may have existed in North America at least 3000 years ago. The first clinical description of RA is credited to Augustin-Jacob Landre Beauvais in his thesis in 1800. Sir Alfred Garrod first introduced the term 'rheumatoid arthritis' in 1876. Paleopathologic studies have identified bone erosions consistent with RA in many Native American skeletons dating as far back as 6500 years ago in a circumscribed area of the Mississipi Basin. Rheumatic diseases have a major impact on individuals and societies,

and economic costs in all countries. Rheumatoid arthritis is prevalent worldwide among all races. Studies indicate a point prevalence of between 0.5 to 1%. Throughout the world, there are pockets of ethnic groups that have a much higher incidence of rheumatoid arthritis. North American Indians are one of such groups. In one geographic area, for instance, nonIndian populations had an RA prevalence of 0.9 to 1.1% between 1986 and 1994, whereas the prevalence in Algonquian Indians in the same region ranged from 2 to 2.1% and the disease onset was 12 years earlier in the Indian population.

II. Systemic lupus erythematosus [3](SLE)

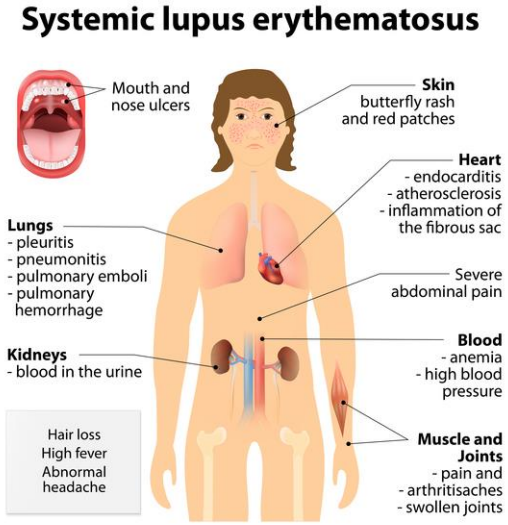

Fig. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a large spectrum of immunological abnormalities with the production of autoantibodies, resulting in widespread inflammation and tissue and organ damage. The disease is clinically heterogeneous and has a course of alternate active and quiescent stages. It is more commonly seen to affect adult women of child bearing age than men and also less frequent among children.

The prevalence rate of the disease varies depending on ethnicity, demography and environment and has been reported to be 14.6-122 per 100,000 populations in United States of America (USA) and 30-50 per 100,000 populations in Asia. In USA, 0.0498% (50,249 cases) of total death reported from 1968 to 2013 was related to the complications of SLE. The incidence rate of SLE in the United Kingdom (UK) from 1999 to 2012 was 0.0049 % per year but there is a scarcity of information regarding incidence rate in India. A study has reported an incidence rate of 1.3% per year in rheumatology clinics of large cities of India.

The disease is complex as it affects multiple organs including skin, joints, haematopoietic system, kidneys, lungs and central nervous system (CNS). However, skin rash, renal complications, arthritis and hematological manifestations are more frequent in SLE. Renal complications and multiple organ failure were the major causes of mortality in SLE . Multiple clinical manifestations accumulate in the course of the disease. Thus the clinical complexity of the disease increases along with the increase in disease duration.

More than 100 autoantigen-specific antibodies are involved in SLE disease but antinuclear antibodies (ANA) especially anti-double stranded deoxyribonucleic acid (dsDNA), anti-nucleosome, anti-histone and anti-Smith (Sm)D1 antibodies show more specificity to SLE. Sjögren's-syndrome associated antibodies, anti-Sjögren'ssyndrome related antigen A (SSA)/Ro60, anti-Ro52/tripartite motif-containing protein 21 (TRIM21) and anti- Sjögren's-syndrome related antigen B (SSB)/La are also found to associate with SLE. Laboratory and serological abnormalities like high C-reactive protein (CRP) levels, high erythrocyte sedimentation rate (ESR), high creatinine levels and low complement levels are also found in the disease.

Various factors are involved in the development of the disease such as functional defects of the innate immune components, loss of self immune-tolerance, hyperactivation of B and T cell responses, defect in clearance of immune complexes and apoptotic bodies and defect in immune regulatory pathways. These defects, at the same time, can occur due to multiple SLE susceptible genes, sex hormones, epigenetic mechanisms and environmental factors including sunlight, drugs and infections. SLE susceptible genes can be divided into three categories; namely

(i) Genes involved in toll-like receptor (TLR)/interferon (IFN) signaling,

(ii) Genes involved in signal transduction on B, T and antigen presenting cells (APCs) and

(iii) Genes involved in immune complex clearance mechanism .

a complex model of disease genetics, in which multiple genes have small effects hat together contribute to the disease phenotype. SLE develops when genetically predisposed people encounter environmental agents which trigger disease onset and flares.

I. **Scleroderma**[4]

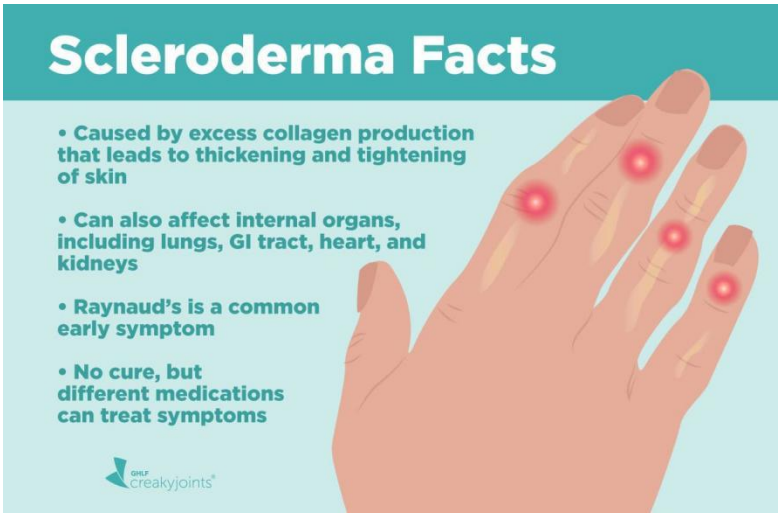

Fig.Scleroderma

Scleroderma (systemic sclerosis) is a complex disease in which extensive fibrosis, vascular alterations, and autoantibodies against various cellular antigens are among the principal features. There are two major subgroups in the commonly accepted classification of scleroderma: limited cutaneous scleroderma and diffuse cutaneous scleroderma.In limited cutaneous scleroderma, fibrosis is mainly restricted to the hands, arms, and face. Raynaud's phenomenon is present for several years before fibrosis appears, pulmonary hypertension is frequent, and anticentromere antibodies occur in 50 to 90% of patients. Diffuse cutaneous scleroderma is a rapidly progressing disorder that affects a large area of the skin and compromises one or more internal organs.

Scleroderma can lead to severe dysfunction and failure of almost any internal organ. Here, too, there is considerable heterogeneity. Involvement of visceral organs is a major factor in determining the prognosis. The kidneys, esophagus, heart, and lungs are the most frequent targets. Renal involvement can be controlled by angiotensin-converting–enzyme inhibitors. Severely debilitating esophageal dysfunction is the most common visceral complication, and lung involvement is the leading cause of death.

II. **Primary Sjogrens's syndrome**[5]

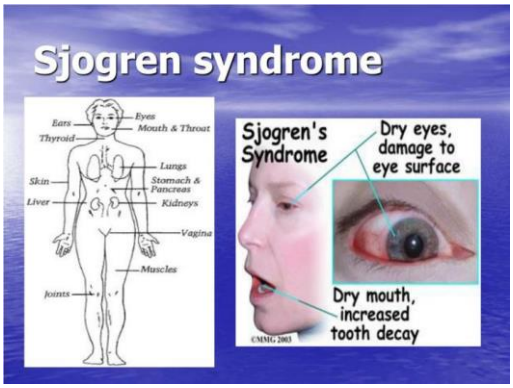

Fig.Primary Sjogrens's syndrome

Sjogren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. The common histolopathological feature of all organs affected is a potentially progressive lymphocytic infiltration. Salivary glands are the most studied organs because they are

affected in almost all patients and are easily accessible. Microscopic examination of the salivary glands reveals a benign lymphoepithelial lesion, characterized by lymphocytic replacement of the salivary epithelium and the presence of epimyoepithelial islands composed of keratin-containing epithelial cells. The predominant cells in the minor labial salivary gland infiltrates are T cells, with a bias towards CD4þ cells rather than CD8þ suppressor cells (CD4/CD8 ratio of 3:1–5:1). B cells constitute approximately 20% of the total infiltrating population, while natural killer (NK) cells are observed less often (5%).

The aetiopathogenesis of primary SS is probably a sequential, multistep process that leads to selective damage of the exocrine glands, with consequent target organ dysfunction. Although the exact mechanisms involved in this aetiopathogenic process are not well known, the autoimmune origin of the disease (autoimmune epithelitis) is probably the aetiopathogenic hypothesis most commonly postulated in primary SS. In this review we have summarized the current concepts on autoimmune aetiopathogenesis of primary SS and reviewed alternative aetiopathogenic mechanisms that have recently been postulated.

III. Polymyositis[6]

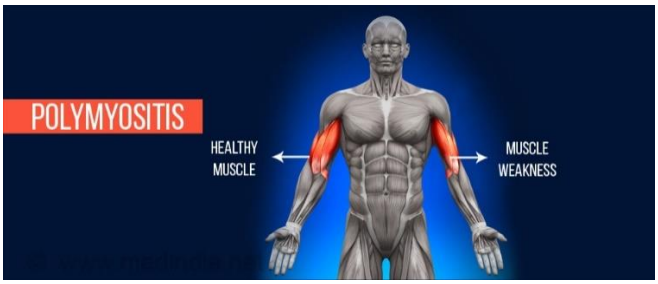

Fig.Polymyositis

Polymyositis is a term that was used traditionally to denote all idiopathic inflammatory myopathies that were not dermatomyositis or sporadic inclusion body myositis, but it is now a controversial entity with questionable specificity. Polymyositis is frequently misdiagnosed, as it lacks a unique clinical phenotype. The most common disease misdiagnosed as Polymyositis is sporadic inclusion body myositis, which is suspected retrospectively in many cases of presumed Polymyositis that have not responded to therapy. Polymyositis may also be diagnosed incorrectly in cases of dermatomyositis, all idiopathic inflammatory myopathies, overlap syndrome associated with a connective tissue disease, muscular dystrophies, myalgia syndromes, or toxic and endocrine myopathies. For these reasons, old case series utilizing Bohan and Peter criteria to identify Polymyositis patients are unreliable and provide an inaccurate and contaminated clinical picture of Polymyositis. Traditionally, Polymyositis is described as presenting with weakness of the proximal muscles that evolves over weeks to months and affects adults, but rarely children.

Environmental Factor [1]: -

- **Gender:**

The prevalence of RA is clearly higher in females, the estimated ratio being ~2.5:1. It is assumed that the risk for the higher incidence of RA among women is related to sex hormones. Estrogens have a generally stimulatory effect on the immune system, and this may be a factor in the increased female-to-male ratio. The relative risks of developing RA in women appear to fluctuate with different stages of the reproductive cycle throughout their lives, from menarche to menopause. Oral contraceptives may protect women from developing more severe disease.

- **Age:**

An age associated increase in the prevalence of RA has also been observed in both males and females.

- **Education level:**

There is an increased mortality and morbidity from RA in patients, particularly women, who have had less formal education.

- **Climatic conditions:**

In the Northern hemisphere, the onset of RA is more frequent in winter than in summer. In several seasons, the onset of RA from October to March in the Northern hemisphere was found to be twice as frequent as in the other 6 months.

- **Infectious Agents:**

Epstein-Barr virus (EBV) has been linked to RA for more than 25 years. Eighty percent of the patients with RA have a circulating antibody directed against antigens specific for EBV and the autoantibody response in RA enhances the response to these antigens. Epstein-Barr virus is well established as a polyclonal activator of B lymphocytes, resulting in the overproduction of immunoglobulins including rheumatoid factor. Mycobacteria have often been linked to rheumatoid arthritis. Patients with RA have elevated levels of antibodies to heat-shock proteins from recombinant mycobacteria.

- **Endogenous Factors:**

Cartilage may be invaded and destroyed by the proliferative synovitis and an immune response mounted against the epitopes on degraded portions of collagen (Jasin HE, 1983). The collagen-antibody complexes, along with rheumatoid factor-IgG complexes, can precipitate within superficial layer of cartilage and serve as chemoattractant for the invasive tissue. Collagen and IgG are the endogenous proteins implicated in rheumatoid arthritis. One of the hypotheses for RA states that RA is not caused by the development of antibodies to collagen (Type II) found in articular cartilage, but rather synovitis and the centripetal polarization of destructive arthritis leads to the disease. Elevated titers of antibody to both naïve and denatured forms of Type II collagen are found in the serum of patients with rheumatoid arthritis.

- **Genetic Factors:**

Studies have indicated a genetic predisposition for rheumatoid arthritis. Severe RA is found at approximately four times the expected rate in first-degree relatives of individuals with disease associated with the presence of rheumatoid factor, and ~10% of patients with RA have an affected first-degree relative. In addition to age and sex-related predisposing factors, a number of other factors, including socio-economic status, education and stress have been suggested to play predisposing roles.

B. Organ specific or localized autoimmune diseases

As the name indicates in these cases the autoimmunity involves a particular organ. One best studied organ is thyroid and examples are Hashimoto's disease which affects thyroid gland causing lymphadenoid goitre and the other is Graves disease causing thyrotoxicosis. Anti thyroglobulin antibodies are produced in both these cases and these can be shown in sera of the patients by various tests. However, the pathology in the two is different and so are the resulting symptoms. In Hashimoto' goitre there is hypothyroidism and in Graves disease there is hyperthyroidism. Another example is Addison's disease in which the adrenal glands are affected. There is lymphocytic infiltration of the adrenal glands and production of antibodies directed against zona glomerulosa. Other diseases include autoimmune disease of eyes, brain, skin and many others. In organ specific autoimmune diseases the implicated antigens and the autoimmunity are restricted to specific organs in the body a. Type I diabetes

b. Goodpasture's syndrome

c. Multiple sclerosis

d. Grave's disease

e. Hashimoto thyroiditis

f. Myasthenia gravis

a. Type I diabetes[7]:

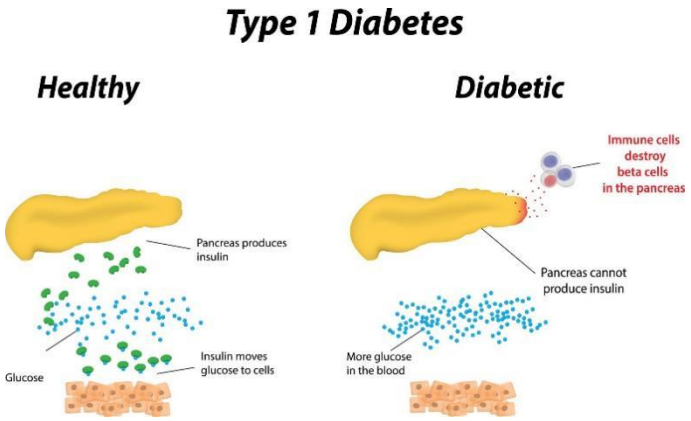

Fig.Type I diabetes

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by increased blood glucose levels (hyperglycaemia), which are due to the insulin deficiency that occurs as the consequence of the loss of the pancreatic islet β-cells1–4. T1DM is one of the most common endocrine and metabolic conditions occurring in childhood. In the vast majority of patients (70–90%), the loss of β-cells is the consequence T1DMrelated autoimmunity (concomitant with the formation of T1DMassociated autoantibodies); these patients have autoimmune T1DM (also known as type 1a diabetes mellitus)

In a smaller subset of patients, no immune responses or autoantibodies are detected, and the cause of βcell destruction is unknown (idiopathic T1DM or type 1b diabetes mellitus); this type has a strong genetic component5 Unless otherwise specified, the term T1DM refers to autoimmune T1DM in this Primer.

Type 1 diabetes mellitus (T1DM), also known as autoimmune diabetes, is a chronic disease characterized by insulin deficiency due to pancreatic β-cell loss and leads to hyperglycaemia. Although the age of symptomatic onset is usually during childhood or adolescence, symptoms can sometimes develop much later. Although the aetiology of T1DM is not completely understood, the pathogenesis of the disease is thought to involve T cell-mediated destruction of β-cells. Islet-targeting autoantibodies that target insulin, 65kDa glutamic acid decarboxylase, insulinoma-associated protein 2 and zinc transporter 8 — all of which are proteins associated with secretory granules in β-cells — are biomarkers of T1DM-associated autoimmunity that are found months to years before symptom onset, and can be used to identify and study individuals who are at risk of developing T1DM. The type of autoantibody that appears first depends on the environmental trigger and on genetic factors.

a. Goodpasture's syndrome[8]:

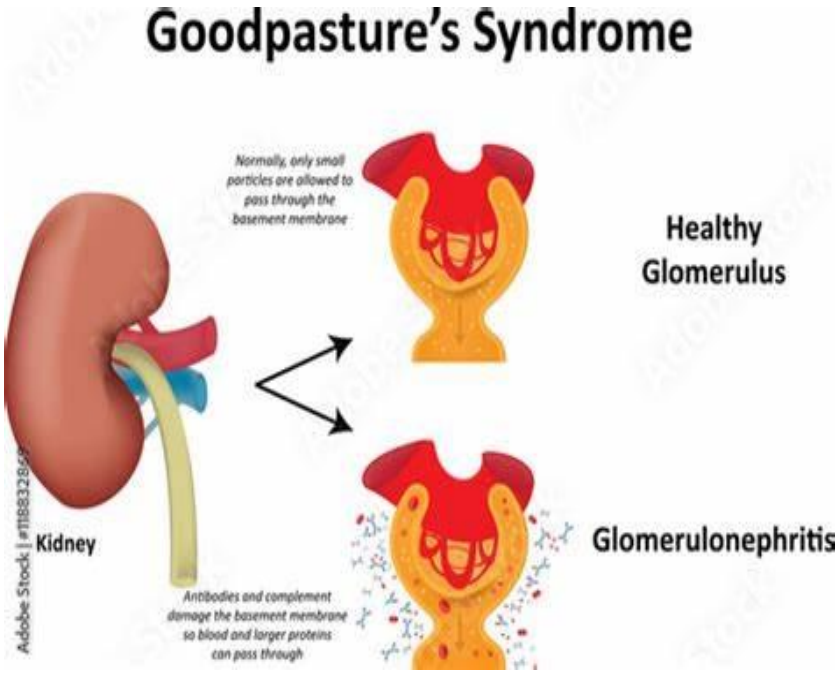

Fig.Goodpasture's syndrome

Goodpasture's syndrome (GS) is a rare disease, identified by Dr. Ernest Goodpasture in 1919. It is an organ-specific autoimmune disease that is mediated by anti-glomerular basement membrane (anti-GBM) antibodies and has pathology characterized by crescentic glomerulonephritis with linear immunofluorescent staining for IgG on the GBM. It typically presents as acute renal failure caused by a rapidly progressive glomerulonephritis, accompanied by pulmonary hemorrhage, that may be life-threatening. Other acronyms and names include Goodpasture's disease, antiGBM disease and crescentic glomerulonephritis type 1. Numerous reports of single patients with this disorder, as well as small case series, have been published. There is the lack of systematic data on GS.

a. Multiple sclerosis[9]:

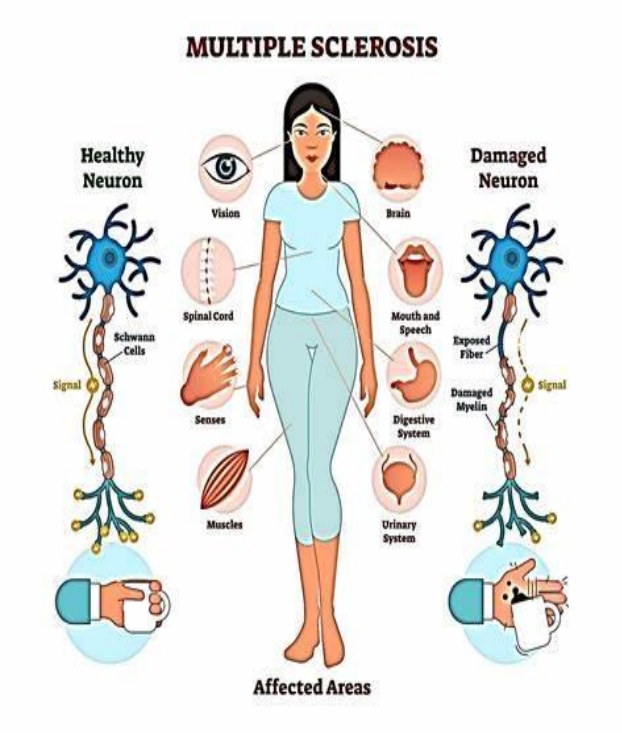

Fig.Multiple sclerosis

Multiple sclerosis (MS) is the commonest non-traumatic disabling disease to affect young adults. There is increasing incidence and prevalence of MS in both developed and developing countries, the underlying cause of which remains uncertain. MS is a complex disease; many genes modestly increase disease susceptibility in addition to several well defined environmental factors, in particular vitamin D or ultraviolet B light (UVB) exposure, Epstein-Barr virus (EBV) infection, obesity and smoking.MS has historically been classified as an organ specific T-cell mediated autoimmune disease. However, the success of B-cell targeted therapies challenges the standard T-cell autoimmune dogma. It is traditionally viewed as a two-stage disease, with early inflammation responsible for relapsing-remitting disease and delayed neurodegeneration causing nonrelapsing progression, i.e. secondary and primary progressive MS. The emergence of increasingly effective biological therapies and an active approach to treating MS, in particular treating to a target of no evident disease activity (NEDA), are changing the long-term outcome for people with MS (pwMS). More aggressive immune reconstitution therapies (IRTs), that result in a proportion of pwMS entering long-term remission, offer a small number of pwMS a potential cure. Recent positive trials of DMTs in 'progressive MS' offer those with more advanced MS the hope of slowing their disease progression, with preservation of residual function. The fact that treatments appear to work at multiple stages in the disease course significantly challenges the traditional 2-stage view of the natural history of MS.

. **Grave's disease[10]:**

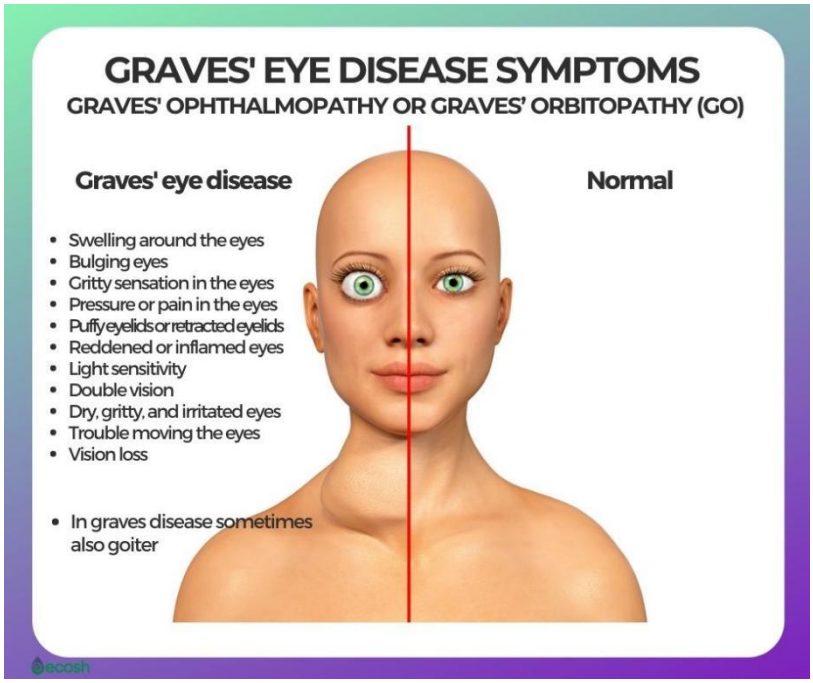

Fig.Grave's disease

Graves first identified the associationof goiter, palpitations, and exophthalmos in 1835, although Caleb Parry had published details of a case 10 years earlier. The discovery of a thyroid-stimulating factor that was not thyrotropin in the serum of patients with Graves' hyperthyroidism1 was followed by the identification of this stimulator as an IgG antibody.2 It is now clear that Graves' hyperthyroidism is caused by these thyroid-stimulatingantibodies, which bind to and activate the thyrotropin receptor on thyroid cells.3 Graves' disease also affects the eyes (Graves' ophthalmopathy) and the skin(localized dermopathy or myxedema), but the causes of these less common components of the disease are not known.

e. Hashimoto' thyroiditis[11]:

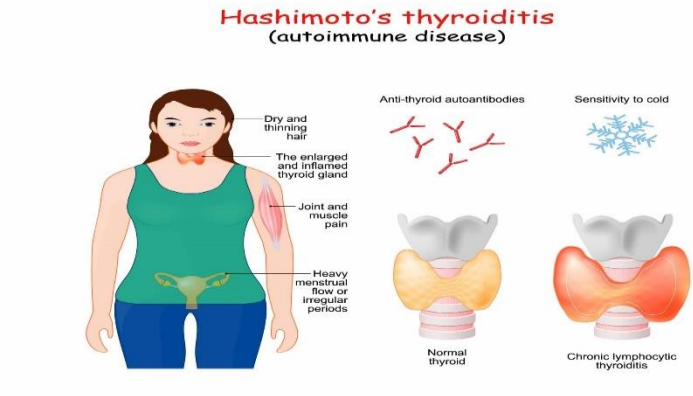

Fig.Hashimoto' thyroiditis

Hashimoto's thyroiditis (HT) is a chronic autoimmune thyroid disease caused by an interaction between genetic factors and environmental conditions, both of which are yet to be fully understood. The management of HT depends on its clinical manifestations, commonly including di; use or nodular goiter with euthyroidism, subclinical hypothyroidism and permanent hypothyroidism. However, in most cases of patients with HT, lifelong levothyroxine substitution is required thyroglontibodies (Tg-Ab)], and with lymphocytic in> ltration. Its prevalence depends on age (more frequently appears between 45-55 years), gender (4-10 times more frequent in females than in males) and race (more common in whites than in blacks, hispanics and asians). Aside from smoking, which decreases the risk for HT, other factors like alcohol, stress, pregnancy and drug use e.g. iodinbulin ae, interferon- immunomodulatory agents such as ipilimumab, pembrolizumab, nivolumab, and the humanised monoclonal antibody to CD52 alemtuzumab may in genetically predisposed individuals, initiate the development of HT. Although the exact mechanism of progressive thyroid tissue destruction is not clear, HT is regarded as a disorder of T cell-mediated immunity, caused by an interaction between susceptibility genes and environ-mental factors, the research of which is still inconclusive.

f. Myasthenia gravis[12]

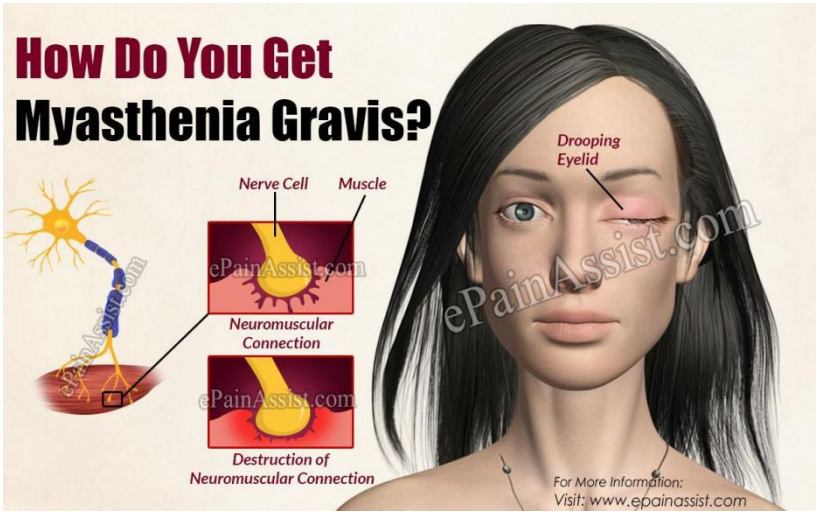

Fig.Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune syndrome caused by the failure of neuromuscular transmission, which resultsfrom the binding of autoantibodies to proteins involved in signaling at the neuromuscular junction (NMJ). These proteins include the nicotinic AChR or, less frequently, a muscle-specific tyrosine kinase (MuSK) involved in AChR clustering.

Much is known about the mechanisms that maintain self tolerance and modulate anti-AChR Ab synthesis, AChRclustering, and AChR function as well as those that cause neuromuscular transmission failure upon Ab binding. This insight has led to the development of improved diagnostic methods and to the design of specific immunosuppressive or immunomodulatory treatments.

C. Haemolytic autoimmune disease.[13]

Auto antibodies are formed against RBCs leading to autoimmune haemolytic anaemia; auto antibodies may form against platelets resulting in autoimmune thrombocytopaenia; and formation of anti leucocyte antibodies resulting in autoimmune leucopaenia.

a. Autoimmune Haemolytic Anaemia[14]:

Autoimmune haemolytic anaemia (AIHA) can be defined as a reduced haemoglobin concentration, resulting from a shortened red cell lifespan, caused by autoantibodies directed against antigens on the patient's erythrocytes. Although AIHA is usually considered to be a well defined clinical syndrome, the more closely cases are examined the more obvious it becomes that severe anaemia is one extreme of a fundamental disturbance of immune homeostasis; at the other end of the spectrum are those in whom erythrocyte autoantibodies are the only abnormality found.

b. Autoimmune Thrombocytopaenia[15]:

Immune thrombocytopaenic purpura (ITP), historically known as morbus haemorrhagicus maculosus or Werlhof's disease, after the name of the physician who described it for the first time in 1739, was once considered an idiopathic condition of unclear origin. Nowadays, the complex immune-mediated thrombocytopaenic pathogenesis of ITP is much better understood and should not be regarde d as being so mysterious.1 Remarkably, in 1951 WJ Herrington at Washington University daringly self-infused blood from a patient with an unexplained decreased platelet count and subsequently infused other healthy volunteers, leading to a drop in their circulating platelet levels.2,3 Several years later, that infused factor circulating in the blood was revealed to be an immunoglobulin G (IgG).4 The clinical presentation of ITP is defined by less than 100,000 platelets per ml, typically without signs or symptoms of leucopaenia and/or anaemia as long as an overlapping disease is absent.

c. **Autoimmune Leucopaenia[16]**:

The terms "autoimmune leukopenia," "autoimmune granulocytopenia," and "autoimmune Neutropenia" are often used synonymously to describe conditions in which autoantibodies to mature neutrophils, or their precursors, lead to cell destruction and a reduced blood neutrophil count. Leukopenia is generally defined as a reduction in the total white blood cell count to less than 4,000 cells per deciliter; Neutropenia is defined as a neutrophil count of less than 1,800 cells per deciliter. Neutropenia has numerous causes and mechanisms; the most frequent cause is reduced cell production by the bone marrow. Neutropenia also occurs because of abnormalities in the distribution of cells between the circulating and marginated pools of cells in the blood and accelerated cell destruction. Autoimmune leukopenia can be caused by any of these mechanisms.

D. CAUSES OF AUTOIMMUNE DISEASES

Let us understand why normally immune response does not occur against our own tissue antigens. This is due to "Tolerance to self-antigens" which is acquired by various mechanisms. Failure in immune recognition of self and injury of self-tissues (autoimmunity) results from a loss of self-tolerance. Let us discuss the mechanisms of self-tolerance and how it is broken down to result in autoimmunity.

i. Mechanisms of self-tolerance

One mechanism is that the clones of lymphocytes which act against self-antigens are deleted. This is the "clonal deletion" theory. Clonal deletion is mediated by ubiquitous self-antigens. The second is inactivation of developing lymphocytes so our immune system becomes self-tolerant, no activation of immunity against self-antigens as specific lymphocytes are either deleted or inactivated. Clonal inactivation can be mediated by tissue-specific antigens.

ii. Peripheral T cell tolerance mechanisms

These are explained below:

- Immunological Ignorance: Very few self proteins contain peptides that are presented by a given MHC molecule at a level sufficient for T cell activation, Autoreactive T cells are present but not normally activated.
- Suppressor or regulatory T cells: mediate active suppression of autoreactive cells
- Immunologically privileged sites: no lymphatic drainage or non-vascularized areas; presence of immunosuppressive factors.
-

iii. Peripheral B cell tolerance mechanisms

- Contact with soluble antigens: this leads to downregulation of surface IgM, and so there is inhibition of signaling resulting in anergic (non-reactive) cells and so no immune response occurs against these soluble antigens, there is tolerance to these antigens.
- Another mechanism of self-tolerance is the Fas-mediated apoptosis (programmed cell death) of anergic B cell following secondary encounter with CD4 T cell.

E. Implants

An implant is a medical device manufactured to replace a missing biological structure, support a damaged biological structure, or enhance an existing biological structure. Medical implants are human-made devices, in contrast to a transplant, which is a transplanted biomedical tissue. The surface of implants that contact the body might be made of a biomedical material such as titanium, silicone, or apatite depending on what is the most functional.[1] In some cases implants contain electronics, e.g. artificial pacemaker and cochlear implants. Some implants are bioactive, such as subcutaneous drug delivery devices in the form of implantable pills or drug-eluting stents.

Types of Implants:

- Breast Implants
- Cerebral Spinal Fluid (CSF) Shunt Systems
- Cochlear Implants
- Essure Permanent Birth Control
- Hernia Surgical Mesh Implants
- Metal-on-Metal Hip Implants
- Phakic Intraocular Lenses
- Urogynecologic Surgical Mesh Implants

F. Advantages and disadvantages of implants

Advantages:

- Controlled drug delivery for over a long time
- Improve patient compliance
- Targeted drug delivery
- Bypass first pass metabolism

- Decrease side effect
- Improve stability of drug
- Improve availability of drug

Disadvantages:

- Mini-surgery is needed (painful).
- Uneasy to simply discontinue the therapy
- Local reactions
- Inadequate release

Marketed Preparations

A. Dental Implants:

Dental implants are replacement tooth roots. Implants provide a strong foundation for fixed (permanent) or removable replacement teeth that are made to match your natural teeth.

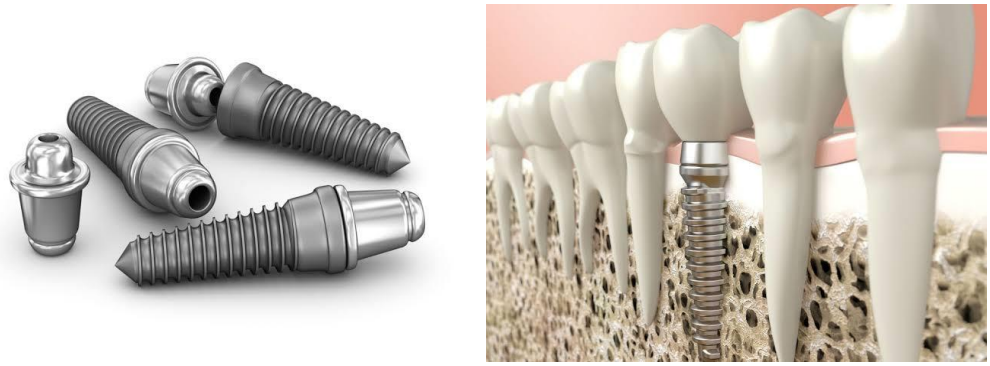

Fig. Dental Implants

Advantages

- **Improved appearance.** Dental implants look and feel like your own teeth. And because they are designed to fuse with bone, they become permanent.
- **Improved speech.** With poor-fitting dentures, the teeth can slip within the mouth causing you to mumble or slur your words. Dental implants allow you to speak without the worry that teeth might slip.
- **Improved comfort.** Because they become part of you, implants eliminate the discomfort of removable dentures.
- **Easier eating.** Sliding dentures can make chewing difficult. Dental implants function like your own teeth, allowing you to eat your favorite foods with confidence and without pain.
- **Improved self-esteem.** Dental implants can give you back your smile and help you feel better about yourself.
- **Improved oral health.** Dental implants don't require reducing other teeth, as a tooth-supported bridge does. Because nearby teeth are not altered to support the implant, more of your own teeth are left intact, improving long-term oral health. Individual implants also allow easier access between teeth, improving oral hygiene.
- **Durability.** Implants are very durable and will last many years. With good care, many implants last a lifetime.
- **Convenience.** Removable dentures are just that; removable. Dental implants eliminate the embarrassing inconvenience of removing dentures, as well as the need for messy adhesives to keep them in place.

B. Breast Implants:

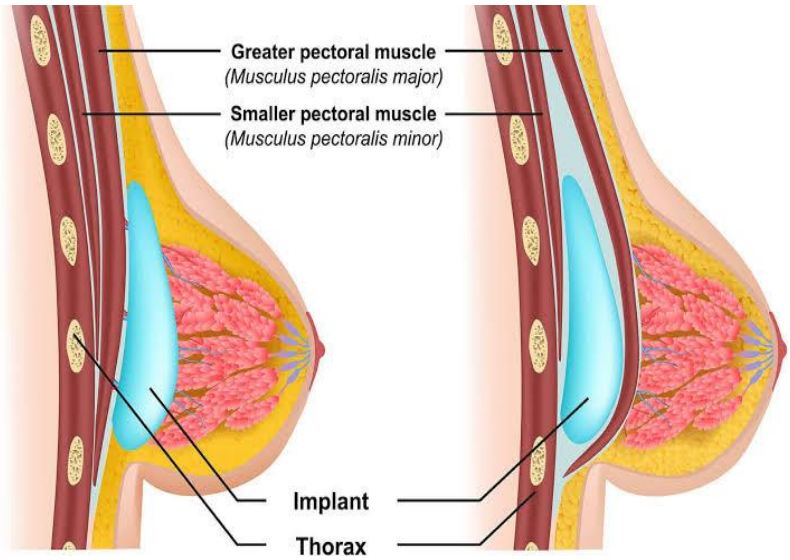

Fig.Breast Implants

To insert the breast implant, your plastic surgeon will make a single cut (incision) in one of three places:

- The crease under your breast (inframammary)
- Under your arm (axillary)
- Around your nipple (periareolar)

After making an incision, the surgeon will separate your breast tissue from the muscles and connective tissue of your chest. This creates a pocket either behind or in front of the outermost muscle of the chest wall (pectoral muscle). The surgeon will insert the implant into this pocket and center it behind your nipple.

Saline implants are inserted empty and then filled with sterile salt water once they're in place. Silicone implants are pre-filled with silicone gel.

When the implant is in place, the surgeon will close the incision — typically with stitches (sutures) — and bandage it with skin adhesive and surgical tape.

C. Bone Cancer Implant:

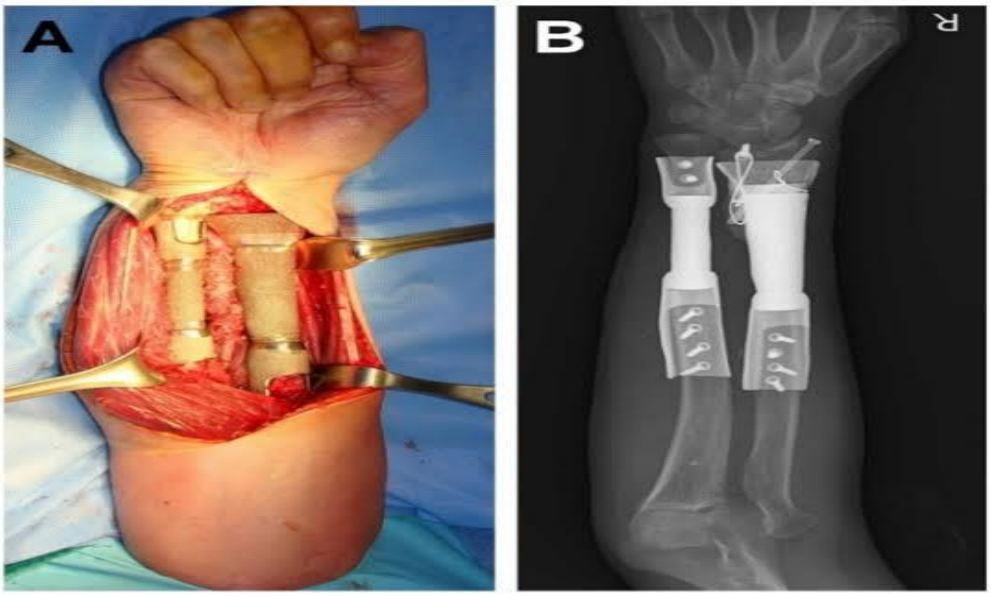

Fig.Bone implant

In Primary surgery Intraoperative photograph and postoperative plain radiograph showing the general configuration of an implant. bone implants of the radius and the ulna. Photographs showing 3D-printed implants of both forearm bones with the host bone models . a volar view of the ulnar implant, and the mesh-structured junctional area of the implants. The indicates the ulnar implant.

Several different kinds of tumors can grow in bones: primary bone tumors, which form bone tissue and can be malignant (cancerous) or benign (not cancerous), and metastatic tumors (tumors that develop from cancer cells that formed elsewhere in the body and then spread to the bone). Malignant primary bone tumors (primary bone cancers) are less common than benign primary bone tumors. Both types of primary bone tumors may grow and compress healthy bone tissue, but benign tumors usually do not spread or destroy bone tissue and are rarely a threat to life.

Primary bone cancers are included in the broader category of cancers called sarcomas. (Soft-tissue sarcomas—sarcomas that begin in muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body, including synovial sarcoma—are not addressed in this fact sheet.)

Primary bone cancer is rare. It accounts for much less than 1% of all new cancers diagnosed.

Cancer that metastasizes (spreads) to the bones from other parts of the body is called metastatic (or secondary) bone cancer and is referred to by the organ or tissue in which it began—for example, as breast cancer that has metastasized to the bone. an estimated 280,000 adults ages 18–64 years in the United States were living with metastatic cancer in bones .

D. Diabeties Implant:

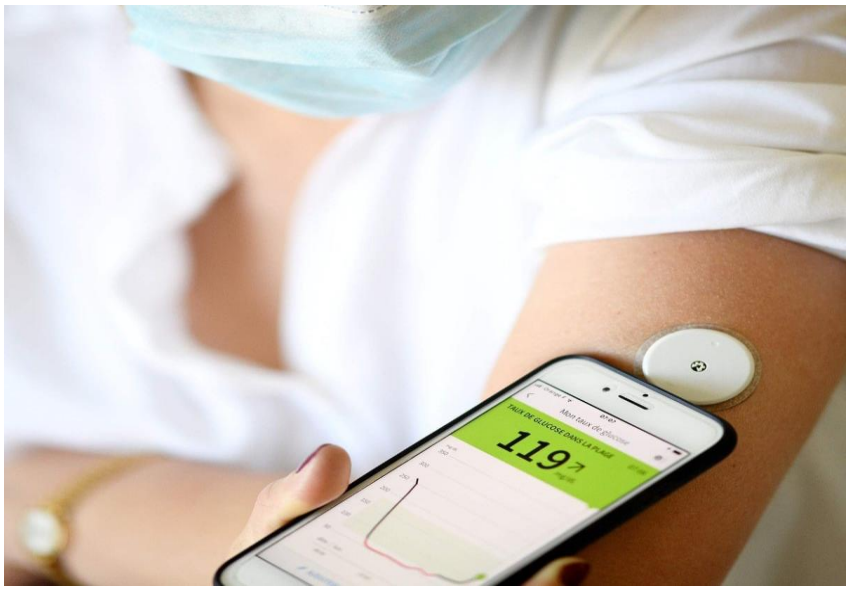

Fig.Diabeties Monitoring

CGM) is wearable technology used to monitor glucose levels at all times. A sensor is placed beneath the arm's or belly's skin and reads interstitial glucose, which is the level of glucose found in the fluid between cells. In younger people it can be placed on the buttocks.

It's designed to take measurements of your glucose levels all day and night and provide a snapshot of your levels at any given time.

Keeping track of trends in how your glucose levels rise and fall throughout the day in real-time aids in the overall management of diabetes because it can give you insight as to where your blood sugar is and where it is going so you can discover patterns and make necessary changes to better balance your blood sugars.

Conclusion:

In conclusion, implant technology has shown promising results in the treatment of autoimmune diseases. The ability to deliver medication directly to the affected area with sustained release has greatly improved patient outcomes, especially in chronic conditions such as rheumatoid arthritis and multiple sclerosis. While there are still challenges to be overcome, such as ensuring biocompatibility and long-term safety, implant technology holds great potential for the future of autoimmune disease treatment. Further research and development in this area could lead to more effective and targeted treatments for patients with autoimmune diseases, ultimately improving their quality of life.

The use of marketed implants for the treatment of autoimmune diseases has shown significant promise in improving the quality of life for patients. The reviewed implants include those designed for the delivery of biologics and those that modulate the immune system through electroceuticals.

Biologic delivery systems have emerged as a major advancement in the treatment of autoimmune diseases. These implants offer targeted delivery of biologics directly to the affected site, allowing for a more effective treatment. This approach has shown promising results in the treatment of rheumatoid arthritis, multiple sclerosis, and Crohn's disease.

Furthermore, electroceuticals, which use electric signals to modulate the immune system, have also shown great potential. These devices work by delivering targeted electrical impulses to specific nerves, which in turn affect the immune response. This approach has been effective in the treatment of inflammatory bowel disease and rheumatoid arthritis.

However, the use of these implants is not without limitations. One major challenge is the potential for adverse effects such as infections, device malfunction, and tissue damage. The long-term safety and efficacy of these implants also need to be further investigated. Moreover, the high cost of these devices and the need for specialized expertise in their implantation are also.

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