SELINUS UNIVERSITY
OF SCIENCES AND LITERATURE

Recent insight on the temporal trend in the incidence and perspective of immunological and rare diseases in the Caribbean (Saint Vincent and the Grenadines in view) from 2014-2018.

by Dr. Adedeji Okikiade

Supervised by

Prof. Mauro Berta P.hD. - Associate Professor Natural Health Science Faculty

Prof. Salvatore Fava Ph.D. Coordinator

A DISSERTATION

Presented to the Department of Natural Health Science

Faculty of Natural Health Science in fulfillment of the requirements for the degree of

Doctor of Philosophy in Regenerative Cellular Therapy (Human pathology).

JUNE, 2020

ATTESTATION

I do hereby attest that I am the sole author of this thesis and that its contents are only the result of the readings and research I have done.

ADEDEJI OKIKIADE. **……..**

Signature:

ABSTRACT

Background/Aims: Immunological diseases are a spectrum of diseases affecting multiple organs and tissues, the study aimed at looking into the recent Insight on the Temporal trend in the Incidence and Perspective of Autoimmune, Immunological and Rare disease in the Caribbean from 2014-2018 (Saint Vincent and the Grenadines in View).

Methods: From 2014 to 2018, individuals with Autoimmune, Immunological, and Rare diseases were identified from the hospital record of Milton Cato Memorial Hospital, which records information on all patients coming in for healthcare services. The incidence was calculated per 1000 person-year and stratified by year, age group, and sex. A structured data extraction tool was employed to extract the data from the hospital record with the aid of an android mobile device using the open data kit (ODK). Incident cases of autoimmune/immunological disease were defined as those without autoimmune/immunological disease in a particular year (e.g., 2014) and the preceding year (e.g., 2013 to 2014) that met the algorithm in that year (e.g., 2015) and the following year (e.g., 2016). Data were analysed using Statistical Package for Social Sciences (SPSS) version 23.0 and R Studio statistical software for analysis. Crude rates, sex- and age-specific rates, standardized rates adjusted for sex and age using the 2014-2018 mid-year population. The Chi-square test was used to test for association. All statistical tests were two-tailed and Level of Confidence was set at 95%, and P values at; 0.05 was considered to be statistically significant.

Results: The mean age of patients with autoimmune/immunological diseases was 35.65 ± 21.16-year old and the median age of 34-year old, almost two-third 218(62.6%) were females. A greater percentage 125(36.0%) had diabetes Mellitus Type 1, 111(32.0%) had Unspecified myopathies, 26(7.5%) had Systemic Lupus Erythematous, only a few rare diseases were identified, this includes Charge disease 1(0.3%), Iridocyclitis 17(4.9%) and ARPKD 2(0.6%). There was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2016 (0.94/1000 person-years). Among sex, there was an annual decrease in the incidence from 2014 to 2018, with a

peak incidence in 2014 for males (0.71/1000 person-years) and a peak incidence in 2016 for females (1.34/1000 person-years). The lowest incidence was noted in 2018 (0.14/1000 person-years) and (0.20/1000 person-years) for both male and female respectively. The incidence of Autoimmune disease peaked within the age group of 31-40 years, after which it declined slowly. The incidence of Autoimmune disease among females was higher compared to that of males with a peak age occurring at 31-35 years.

Conclusions: Sequel to the findings of this study, this study showed that the incidence of autoimmune disease, Type 1 diabetes Mellitus Myopathy/Myositis and SLE in Saint Vincent have decreased in the last decade, whereas the mortality rates of both SLE and Type 1 Diabetes Mellitus have increased.

Keywords: Autoimmune; Immunological; Systemic Lupus Erythematous, Incidence; Saint Vincent and the Grenadines

TABLE OF CONTENTS

List of tables

List of figures

CHAPTER ONE

1.0: INTRODUCTION

More than 80 human diseases are sometimes due to an inappropriate immune system response that results in damage to an individual's organs, tissues, or cells. Autoimmune diseases can affect any part of the body, and have myriad clinical manifestations that can be difficult to diagnose. At the same time, autoimmune diseases share many features related to their onset and progression. In addition, overlapping genetic traits enhance susceptibility to many of the diseases, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family.

1.1: Statement of Problem

Treatments are available for many autoimmune diseases, cures have yet to be discovered. For these and other reasons, the autoimmune diseases are best recognized as a family of related disorders that must be studied collectively as well as individually. While many of these diseases are rare, collectively they affect 14.7 to 23.5 million people in countries like the USA and for reasons unknown their prevalence is rising.

Since cures are not yet available for most autoimmune diseases, patients face a lifetime of illness and treatment. This, therefore, affect QALY and DALY, QALYs (Quality-Adjusted Life Year) and DALYs (Disability-Adjusted Life Year) are common terms used to evaluate and compare, health interventions undergo cost-effectiveness analysis to measure the impact on both the length and the quality of life. QALYs are a measure of years lived in perfect health gained whereas DALYs are a measure of years in perfect health lost.

They often endure debilitating symptoms, loss of organ function, reduced productivity at work, and high medical expenses. And, because most of these diseases disproportionately afflict among sex, and are among the leading causes of death for young and middle-aged individuals they impose a heavy burden on patients, families, and society.

1.2: Justification of Study

Due to gaps in evident literature for the Incidence rates of Autoimmune Diseases in the Caribbean citing Saint Vincent and the Grenadines specifically, this gap gave a recognition that more needs to be done so that we may close the gaps in our knowledge and achieve our overall goal of reducing the rising toll of immunological disease. For example, we need to gain a better understanding of the distribution of these diseases through epidemiologic studies, and of the environmental triggers that contribute to their onset. This research would throw more insight into the genetic and environmental factors contributing to these diseases, and also set a platform to develop effective prevention strategies that arrest the immunological process before it can irreversibly damage the body.

This research sets forth an ambitious and comprehensive research agenda aimed at generating more accurate epidemiologic profiles of immunological diseases; developing a greater understanding of the fundamental biologic principles underlying disease onset and progression; devising improved diagnostic tools; creating more effective interventions; producing public and professional education and training programs.

1.3: General Research Objectives

The study aims at looking into the recent Insight on the Temporal trend in the Incidence and Perspective of Autoimmune, Immunological and Rare disease in the Caribbean from 2014-2018 (Saint Vincent and the Grenadines in View).

1.4: Specific Research Objectives

1. To determine the incidence of autoimmune immunological diseases from 2014 -2018 amongst individuals residing in Saint Vincent and the Grenadines
2. To describe the social demographic characteristics of individuals who have autoimmune immunological diseases from 2014 -2018 in Saint Vincent and the Grenadines
3. To determine the incidence of Diabetes Mellitus Type 1 from 2014 -2018 amongst individuals residing in Saint Vincent and the Grenadines.
4. To describe the social demographic characteristics of individuals who have Diabetes Mellitus Type 1 from 2014 -2018 in Saint Vincent and the Grenadines.
5. To determine the case-mortality from Diabetes Mellitus Type 1from 2014 -2018 in Saint Vincent and the Grenadines.
6. To determine the incidence of Myositis/Myopathies from 2014 -2018 amongst individuals residing in Saint Vincent and the Grenadines.
7. To describe the social demographic characteristics of individuals who have Myositis/Myopathies from 2014 -2018 in Saint Vincent and the Grenadines.
8. To determine the case-mortality from Myositis/Myopathies from 2014 -2018 in Saint Vincent and the Grenadines.
9. To determine the incidence of Systemic Lupus Erythematous (SLE) from 2014 -2018 amongst individuals residing in Saint Vincent and the Grenadines.
10. To describe the social demographic characteristics of individuals who have Systemic Lupus Erythematous (SLE) from 2014 -2018 in Saint Vincent and the Grenadines.
11. To determine the case-mortality from Systemic Lupus Erythematous (SLE) from 2014 -2018 in Saint Vincent and the Grenadines.

1.5: Research Questions:

The study aims to answer some fundamental questions on the Insight on Prevalence, Incidence, and Perspective of Autoimmune, Immunological and Rare disease in the Caribbean from 2014-2018 (Saint Vincent and the Grenadines in View).

Research Questions

1. What is the incidence of autoimmune immunological diseases from 2014 -2018 amongst individuals residing in Saint Vincent and the Grenadines?
2. What are the social demographic characteristics of individuals who have autoimmune immunological diseases from 2014 -2018 in Saint Vincent and the Grenadines?
3. What is the incidence of Diabetes Mellitus Type 1 from 2014 -2018 amongst individuals residing in Saint Vincent and the Grenadines?
4. What are the social demographic characteristics of individuals who have Diabetes Mellitus Type 1 from 2014 -2018 in Saint Vincent and the Grenadines?
5. What is the case-mortality from Diabetes Mellitus Type 1from 2014 -2018 in Saint Vincent and the Grenadines?
6. What is the incidence of Myositis/Myopathies from 2014 -2018 amongst individuals residing in Saint Vincent and the Grenadines?
7. What are the social demographic characteristics of individuals who have Myositis/Myopathies from 2014 -2018 in Saint Vincent and the Grenadines?
8. What is the case-mortality from Myositis/Myopathies from 2014 -2018 in Saint Vincent and the Grenadines?
9. What is the incidence of Systemic Lupus Erythematous (SLE) from 2014 -2018 amongst individuals residing in Saint Vincent and the Grenadines?

10. What are the social demographic characteristics of individuals who have Systemic Lupus Erythematous (SLE) from 2014 -2018 in Saint Vincent and the Grenadines?
11. What is the case-mortality from Systemic Lupus Erythematous (SLE) from 2014 -2018 in Saint Vincent and the Grenadines?

1.6: Research Hypothesis

The research hypothesis postulated for this study is as follows; where

$H_{0:}$ Null Hypothesis

$H_{1:}$ Alternate Hypothesis

H_0: There is no significant higher proportion of females to males who have autoimmune immunological disease from 2014 -2018 in Saint Vincent and the Grenadines.

$H_{1:}$ There is a significantly higher proportion of females to males who have autoimmune immunological disease from 2014 -2018 in Saint Vincent and the Grenadines.

H_0: There is no significant higher proportion of females to males who have Diabetes Mellitus Type 1 from 2014 -2018 in Saint Vincent and the Grenadines.

$H_{1:}$ There is a significantly higher proportion of females to males who have Diabetes Mellitus Type 1 from 2014 -2018 in Saint Vincent and the Grenadines.

H_0: There is no significant higher proportion of individuals ≤ 20 years of age compared to other age groups who have Diabetes Mellitus Type 1 from 2014 -2018 in Saint Vincent and the Grenadines.

H_1: There is a significantly higher proportion of individuals ≤ 20 years of age compared to other age groups who have Diabetes Mellitus Type 1 from 2014 -2018 in Saint Vincent and the Grenadines.

H_0: There is no significant higher proportion of females to males who have Myositis/Myopathies from 2014 -2018 in Saint Vincent and the Grenadines.

H_1 There is a significantly higher proportion of females to males who have Myositis/Myopathies from 2014 -2018 in Saint Vincent and the Grenadines.

H_0: There is no significant higher proportion of females to males who have Systemic Lupus Erythematous (SLE) from 2014 -2018 in Saint Vincent and the Grenadines.

H_1 There is a significantly higher proportion of females to males who have Systemic Lupus Erythematous (SLE) from 2014 -2018 in Saint Vincent and the Grenadines.

H_0: There is no significant higher proportion of individuals ≥ 40 years of age compared to other age groups who have Systemic Lupus Erythematous (SLE)from 2014 -2018 in Saint Vincent and the Grenadines.

H_1: There is a significantly higher proportion of individuals ≥ 40 years of age compared to other age groups who have Systemic Lupus Erythematous (SLE) from 2014 -2018 in Saint Vincent and the Grenadines.

H_0: There is no significant higher proportion of case-mortalities from individuals who have Diabetes Mellitus Type 1 compared to individuals who have Systemic Lupus Erythematous (SLE) and other autoimmune diseases from 2014 -2018 in Saint Vincent and the Grenadines.

$H_{1:}$ There is a significantly higher proportion of case-mortalities from individuals who have Diabetes Mellitus Type 1 compared to individuals who have Systemic Lupus Erythematous (SLE) and other autoimmune diseases from 2014 -2018 in Saint Vincent and the Grenadines.

CHAPTER TWO
LITERATURE REVIEW

2.1: Conceptual/Theoretical Framework of Autoimmune/Immunological Disease

Immunological diseases are a spectrum of diseases affecting multiple organs and tissues. They are mistakenly identified as autoimmune diseases or "autotoxicus", a term designated by Paul Ehrlich (McGonagall D and McDermott MF, 2006). The Immune systems can be categorized into Innate (Natural) immunity and Acquired (Adaptive) immunity, it consists of various elements that were created to protect the human body from both endogenous and exogenous (environmental) sources of harm.

Innate immune systems are the body's non-specific defence mechanisms such as skin, tears in the eyes, cerumen in the ears, lysozyme in the urinary bladder, neutrophils, macrophages, respiratory cilia, alveolar macrophages, dendritic cells, defensins, normal flora, acute phase reactants like complements, lactoferrin, transferrin, interferons, and others include natural killer (NK) cells, fever, low pH and fatty acids in the skin (Warren et al., 2018).

Abnormality of the innate system is technically independent of B and T Lymphocytes. The Innate immune system does not require antibodies or the Major Histocompatibility Complex (MHC) Pathways except when some of the cells such as dendritic cells and macrophages act like antigen-presenting cells (APC) but involves inflammasomes adaptor molecules working via TNF-1 and IL-1ß. The innate immune system is fast-acting, activates the adaptive immune system, and produces chemokines and cytokines but keeps no memory (memory B cells) (Warren et .al 2018).

Immunological malfunction of the innate immune system is generally considered in the category of autoinflammatory diseases as a result in alteration of the cytokines (as in periodic fever), aberrant bacterial sensing (as in Crohn's disease), and tissue microdamage, which can be autosomal dominant or recessive, non-genetic or granulomatous. Auto-inflammatory diseases are rare and rarely discussed as an entity in most literature. Examples of autoinflammatory diseases are Majeed syndrome; Familial Mediterranean fever (FMF)/Ranean fever; Hereditary periodic fever; Cryopyrin associated periodic syndrome (CAPS) like Muckle-Wells syndrome which

is characterized by hearing problems, skin rashes and recurring fever; Hereditary autosomal dominant Hibernian fever; Hyperimmunoglobulin D syndrome (HIDS); TNF-1 receptor-associated periodic syndrome (TRAPS); Periodic fever - Aphthous stomatitis - Pharyngitis - Cervical adenitis (PFAPA) and CANDLE Syndrome (Hawkins PN Ethol 2004, McGonagall D et al., 2006; McDermott MF 1999). Recent studies now partly classify Systemic Onset Juvenile Idiopathic Arthritis, Sweet's syndrome, and Bechet's disease into the category of auto-inflammatory disease or having auto-inflammatory like presentation. Some others include Early-onset sarcoidosis; Biau syndrome; Gout (monogenetic, activation of IL-1ß signalling cascade via NALP3 inflammasome); Chronic recurrent multifocal osteomyelitis; Crohn's disease (NOD-2 protein mutation on the gut); Pyogenic arthritis - Pyoderma gangrenosum - Acne (severe cystic type) (PAPA) syndrome (McGonagall D et al., 2006; Strober W 2006).

There is evidence to support that some of the diseases are strictly auto-inflammatory. In some known immunological and relatively common diseases, the canonical cytokine blockage in auto-inflammatory diseases is a well-documented target therapy to support the hypothesis and understanding that they are purely auto-inflammatory (Hawkins PN Ethol, 2004). Examples of such diseases and their target therapy are highlighted briefly below;

- Gout and FMF: colchicine, which may interfere with inflammasome activation, as well as interference with leukocyte motility
- Crohn disease: anti-TNF with infliximab or adalimumab
- Ankylosing spondylitis and psoriatic arthritis: responsive to all anti-TNF therapies
- TRAPS: Etanercept (anti-TNF)
- Cryopyrinopathies (chronic infantile neurologic, cutaneous and articular syndrome, neonatal-onset multisystem inflammatory disease, Muckle-Wells syndrome): anakinra (anti-TNF and IL-1ß)
- Anti-TNF (etanercept) or IL-1ß blockade with anakinra may be virtually curative in some cases of monogenic autoinflammatory diseases. Colchicine is especially effective in FMF and gout, but not in autoimmunity.

Anti-TNF therapy has revolutionized the management of Crohn disease and ankylosing spondylitis, but conversely, this same anti-cytokine therapy may aggravate some autoimmune diseases, including systemic lupus erythematosus (SLE) and Sjogren syndrome. However, documented evidence shows blocking of B and T lymphocytes is the obvious aim of target therapy in Autoimmune diseases. Examples include SLE being managed with mycophenolate mofetil, azathioprine, and rituximab and Sjogren syndrome using Rituximab (anti-CD20) (McGonagall D and McDermott MF 2006).

Acquired or adaptive immune systems are B and T lymphocytic cells mediated and malfunction of the acquired immune system is generally termed Autoimmune disorders. This accounts for the bulk of immunological disorders diagnosed and discussed in most literature. It is technically different from auto-inflammatory diseases. (Table 2.1)

Variable	Autoinflammatory	Autoimmune
Factors determining disease manifestations	Local tissue factors at disease-prone sites, including tissue trauma, necrosis, mechanical factors, and bacteria or their constituent molecules	Clinical disease expression determined by events taking place in primary and secondary lymphoid tissues, including bone marrow, thymus, lymph nodes, and spleen
	Innate immune activation	Adaptive immune activation
Key theory relating to disease expression	The danger signal theory of Matzinger, with tissue-specific factors determining disease localisation	The major factor determining disease is aberrant SNS discrimination, with breakdown of immunological tolerance
Immunological basis	Genetically related to perturbations of innate immune function, including pro-inflammatory cytokine signalling abnormalities/ bacterial sensing/local tissue abnormalities	Acquired immune perturbation key-to-disease expression
Cellular basis	Expression determined by cells of innate immune system, including neutrophils and macrophages or nonimmune cells	Expression mainly determined by factors affecting B and T cell activity
	Genetic mutations in HPFs, including TRAPS and FMF, affect these cells	Genetic mutations in rare autoimmune diseases affect these cells or their selection in thymus

DOI: 10.1371/journal.pmed.0030297.t002
This table represents some of the key features that allow differentiation of a "pure autoinflammatory disease" from a "pure autoimmune disease." The rare monogenic HPFs are the prototypic autoinflammatory diseases, whereas the prototypes for autoimmune diseases include the polygenic MHC and autoantibody-related diseases, as well as some rare monogenic diseases. SNS, self/nonself.

Table 2.1

The adaptive B cells are transformed into Plasma cells by the helper T cells (Th-2 subsets) which can produce immunoglobulins (IgG, IgA, IgM, IgD, and IgE). These Immunoglobulins have specialized characteristics and shown in an online adapted table below; (Table 2)

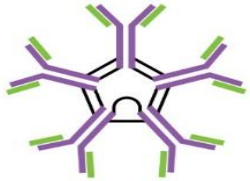
The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

Table 2.2

They are meant to neutralize toxins and viruses, and IgG serves as opsonin on bacteria to allow adequate removal by phagocytes of innate systems. They lack the thymic selective process but they can undergo both negative and positive selective processes to become mature B-cells (differentiating into Lymphoid tissue). The fate of B cells is to either produce antibodies or transformed them into memory B cells when exposed to antigens. They express chemokine receptor CXCR5, which is used to migrate towards the chemokines.
The activation of B-cells is via 2 pathways namely:

1. Short-lived T-cell independent activation mechanism occurs via:

- Systematic activation by bacterial polysaccharides (Innate pathway) because B cells have pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs)
- B cells complement receptor CR2 that recognizes cleavage products of C3b released during complement activation.
- Adjuvants from vaccines activate B cells directly.

2. Long-lived T-cell dependent activation stepwise mechanism is more specific, and the B cells are primarily activated by dendritic cells and T-cells.

This process involves activation of T cells by peptide (antigens) which allows the T cells to be transformed into T follicular helper cells (Tfh) which turns off CCR7 on T cells and turns on CXCR5 on B cells, which allows T cells to migrate to the B -cell follicle. The closeness allows the interaction of T and B cells and exposure of the B cells to the antigen and integration into the endosomes of the B-cells. This interaction turns B-cells to APCs making MHC class 2 molecules on its surface to interact with Tfh cells.

The Tfh cells have CD40 ligand molecules while the B cells have CD40 and IL-21, and this may interact and lead proliferation of B-cells, class switching of immunoglobin genes which is dependent on cytokines and somatic hypermutation which allows B cells to adapt to the foreign triggering antigens.

The adaptive T cells recognize polypeptide only (cognate peptide) binding to T-cell receptors (TCR) when presented in association with Major Histocompatibility Complexes (MHC) on antigen-presenting cells (APC), with the MHC acting like contact stabilizer.LFA-1(integrin) is usually present to further reinforces interaction between the T-cells and the MHC. This interaction allows the release of

C3 signals converting phosphoinositide to IP3 using phospholipase C subsequently leading to calcium influx into the cells which now activates calcineurin (serine phosphatase). Calcineurin moves into the nucleus and activates IL-2 and its receptors. Calcineurin can be blocked by cyclosporin.`

Adaptive T cells can work via:

A. Macrophages and Dendritic cells which can act like APC using CCR7 produced by fibroblast to interact with the T-cells.

B. Specific thymic selection processes, where naïve T cells obtain specific antigenicity (Cluster of differentiation) in the thymus. The cluster of differentiation (CD) can be CD4-T cells recognizing MHC class 2 or CD8-T cells recognizing MHC class 1.

The CD4-T cells have different subsets which are Th-1 cells recruited by IL-12 from APCs and involves recruitment of macrophages, production of interferon-gamma, and formation of granuloma. The Th-17 cells are another group of subsets produced by IL-1, IL-6, and IL-23 from APCs and it involves the production of IL-17, IL-1.IL-6 and neutrophil attracting chemokines thus protecting against bacterial and fungal infections.

The larger subsets of CD4 T cells are the Th-2 cells which protect against parasites/helminths and produce IL-4 and IL-13 meant for transformation of B-cells to IgE producing plasma cells and mucus production respectively. Th-2 also produces IL-5 for eosinophil recruitment and IL-9 for mast cell activation.

C. Natural killer cells using the innate pathway to take care of cancer cells or infections.

Autoimmune disorders are reactions against self-antigen which can be a result of any of the following; cryptic determinants/molecular sequestration, altered glycan theory, molecular mimicry, and the hygiene hypothesis.

To label a disease as autoimmune, it must meet certain criteria postulated by Ernest Witebsky in 1957 and modified in 1994. (Witebsky E 1957).

- Direct evidence from transfer causing antibody or disease-causing T lymphocytes.
- Evidence from clinical clues like signs, symptoms and laboratory evidence (antibody testing, C-reactive protein, serum complements, erythrocyte sedimentation rate, imaging studies or biopsy)

- Indirect evidence based on the reproduction of the autoimmune disease in experimental animals.

Immunological disorders are mostly autoimmune, and are mediated through immunogens which can be:

A. Antigens: highly specific, non-self (foreignness), large molecular weight, structurally complex, multivalent epitopes to bind to antibodies

B. Haptens: Low molecular weight substances like lipids, nucleic acid, drugs, and non-peptide molecules. They are not immunogenic so they require other molecules to be active immunologically active.

Hapten cannot activate helper T-cells induced B cells response so, therefore, no effect on the MHC pathway.

C. Adjuvants: They enhance the immune response to an immunogen without the involvement of antibodies.

Alteration of these pathways and mechanisms of Adaptive T and B cells can lead to autoimmune disease.

To date, more than 80 Autoimmune disorders have been documented. Examples of autoimmune disorders are Hypersensitivity reaction (Allergy), Addison's disease, Systemic lupus erythematosus (SLE), Sjogren's disease, Rheumatoid arthritis, Type-1 Diabetes mellitus, Primary biliary cirrhosis, Systemic sclerosis, Crest's syndrome, Goodpasture disease, Autoimmune hepatitis, Chronic fatigue immune dysfunction syndrome, Churg Strauss syndrome, Berger's disease, Juvenile rheumatoid arthritis, Dermatomyositis/polymyositis, Grave's disease, Post streptococcal glomerulonephritis, Berger's disease (IgA nephropathy), Primary glomerulonephritis, Hashimoto's Thyroiditis, Vitiligo, Myasthenia Gravis, Lambert Eaton disease, Idiopathic thrombocytopenic purpura, Kawasaki disease, Mixed connective tissue disease, Pemphigus Vulgaris, Bullous pemphigus, Polymyalgia rheumatica, Alopecia areata, Pernicious anemia, Psoriasis, Primary sclerosing cholangitis, Raynaud syndrome, Reiter's syndrome, Rheumatic fever, Scleroderma, Still's disease, Takayasu's arteritis, Wegener's granulomatosis, Multiple sclerosis, Celiac disease and Autoimmune hemolytic anemia.

There are some immunological disorders neither classified as autoimmune nor autoinflammatory. These are under active immune system disorders like Severe combined immunodeficiency (SCID), Common variable immunodeficiency (CVID), Acquired immunodeficiency syndrome (AIDS), Chediac Higashi Syndrome, Selective IgA deficiency, Hyper IgM syndrome, Hyper IgE syndrome, Bruton -X agammaglobulinemia, Hay fever, and Asthma.

Mainstay universal treatment of most immunological diseases involves the use of immunosuppressant, immunotherapy, and non-definitive supportive management. Examples of immunosuppressive medications used are corticosteroids (prednisolone), Non-steroidal anti-inflammatory drugs (NSAID: Aspirin, celecoxib), DNA synthesis inhibitors (Methotrexate), Tumor necrotic factor inhibitors (Etanercept, infliximab, Adalimumab), Th-1 and Th-17 pathway inhibitors (Brodalumab, Ustekinumab), Leucocyte migration inhibitors (Natalizumab, Vedolizumab), Calcineurin inhibitors (Cyclosporin), B-cells inhibitors (Rituximab, Octrelizumab), Antimalarial (chloroquine, hydrochroloroquine), Sulfasalazine (inhibits TNF and IL-6 in inflammatory bowel disease) (Li, P., Zheng, Y., & Chen, X. 2017). Other medications used in the treatment of autoimmune disorders with high efficacy and varying side effects are abatacept (anti CD80/CD86) for Rheumatoid arthritis (RA) and Systemic lupus erythematosus (SLE), Tocilizumab (anti IL-6) after anti-TNF treatment failure, Ankinra (anti IL-1) for Rheumatoid arthritis (RA), Ustekinumab (anti-IL-12/23) for Psoriasis, Rituximab (anti-CD20) for SLE and RA and Secukinumab (anti-IL-17) (Li et al., 2017; Wahl C 1998).

Most of these medications present with some undesirable side effects, for instance, traditional non-selective NSAID usage is associated with peptic ulcer disease, duodenal perforation, and gastrointestinal bleeding (Fujita T, 2013). Efficacy and response of autoimmune disease is barely 60 % when anti-TNF medications are used (Roda G, 2016). Other possible reported side effects of anti-TNF are cancer, worsening condition in heart failure patient, development of multiple sclerosis, and reactivation of latent tuberculosis (Balakumar P 2006; Robinson WH 1983).

Though, advancements have been made towards making better drugs with higher affinity, lesser toxicity and are more effective than conventional anti-TNF with the manufacturing of Golimumab a fully-humanized IgG monoclonal antibody against human TNF (Pasut G, 2014). Another one of its types is Certolizumab pegol, a humanized antibody with the structure of polyethylene glycolated Fab fragment with more potent anti-TNF due to its unique structure (Desai R.J, 2012).

The current trend in medical science advancement in the future use of regenerative medicine for the care of immunological disease coupled with the increased awareness of stem cells in the management of immunological diseases is now becoming acceptable among

researchers and clinicians. It is important to understand immunological diseases because of the growing trend of successful stem cell treatment in the management of the diseases. Stem cells are progenitor cells with the ability to differentiate into different types of human cells. They can undergo distinct multilineage proliferation and differentiation and capability to self-renew. There are 2 main broad classifications of stem cells based on the source namely; embryonic stem cells and adult stem cells, but based on trans-differentiation it can be unipotent, multipotent, pluripotent or totipotent (Mahal R. S. (2016).

The classification is based on the trans-differentiation and stemness of these cells which primarily depend on the pluripotency factors like OCT4, cMYC, KLF44, NANOG, and SOX2 (Thomson M, 2011).

1. Embryonic stem cells

a. Embryo (Zygote): This is mainly sourced from an embryo (totipotential) at about 3 days after fertilization and capable of differentiating into 100s of cells including placenta and umbilical cord(Extra-embryonic tissues).The zygote (totipotential) can differentiate into whole organism, while the inner cell mass of the embryo is technically pluripotential like the blastocysts. (Fortier L.A, 2005).

b. Blastocysts: Sourced around 4 to 5days, and are pluripotential stem cells, but cannot differentiate into placenta and umbilical cord. (Figure 2.1)

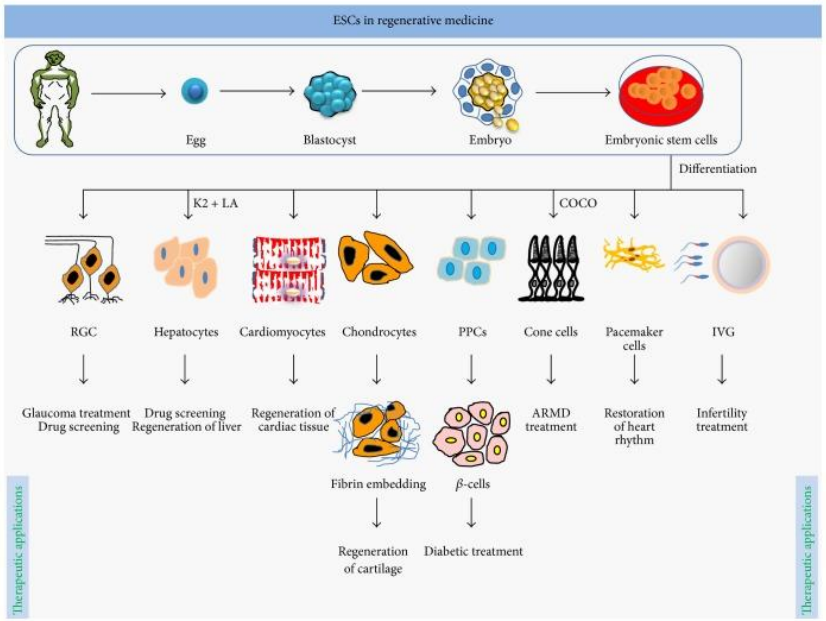


Figure 2.1 Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/

2. Adult Stem cells

This is mostly multipotential stem cells, therefore it gives rise to specific tissues. The stem cells mostly used in clinical medicine are hemopoietic stem cells, which give rise to all types of blood and immune system cells and are mostly sourced from bone marrow, umbilical cord blood, and rarely from peripheral blood. Some are capable of trans-differentiation which is a process characterized by the differentiation of a progenitor cell into a cell line other than that from which it originated. For instance, the generation of neural tissues from bone marrow is an example of trans-differentiation (Efimenko, A. Y, 2015).

Another type of adult stem cell is mesenchymal stem cells, observed in cardiac myocytes, and are pluripotent in nature proving lots of success in the treatment of myocardial infarction. Also, endothelial progenitor cells derived from bone marrow have a role to play in endothelial repair and limit cardiovascular disease progression (Hill JM, Zalos G, 2003).

In the application of stem cell therapy (regenerative medicine), we can categorize stem cells as embryonic stem cells (ESCs), tissue-specific progenitor stem cells (TSPSCs), mesenchymal stem cells (MSCs), umbilical cord stem cells (UCSCs), bone marrow stem cells (BMSCs), and induced pluripotent stem cells (iPSCs) (Ranjeet Singh Mahala, 2016). The use of stem cells in medical science cannot be overemphasized especially in cardiovascular disorders, immunology and aging (Figure 2). We can use autologous, allogeneic and syngeneic stem cells in the induction of tissue regeneration, fixing immunological disorders, killing cancerous cells and pathogens but must be prepared for host versus graft rejections by proper human leucocyte antigens (HLA) typing for tissue and organ transplant as well as the use of immune suppressant administrations (Petersdorf E. W,2007).

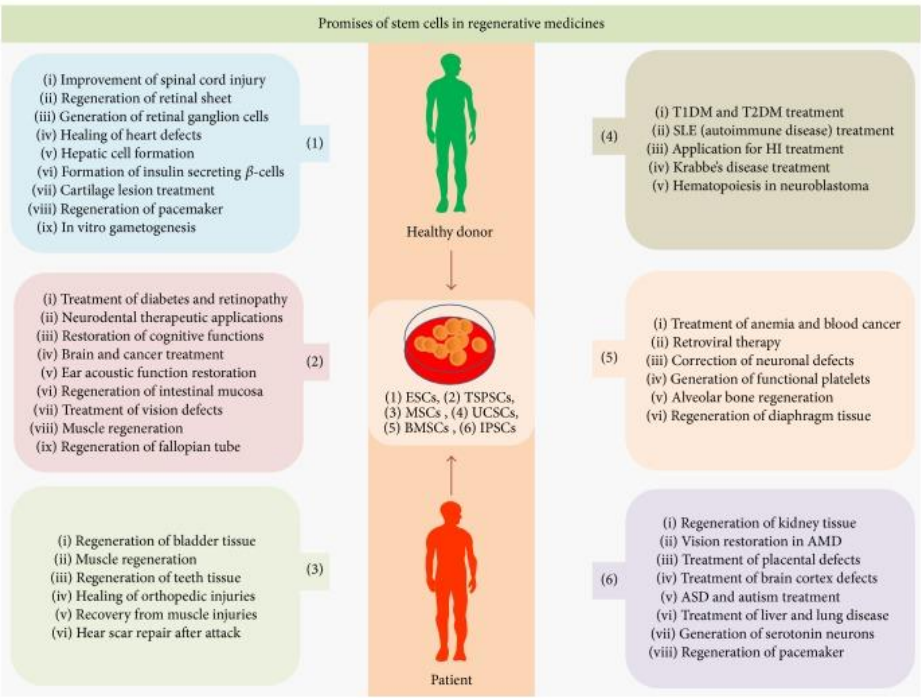


Figure 2.2

Note: AMD/ARMD -age-related macular degeneration, T1DM-TYPE 1 Diabetes mellitus, T2DM-type 2 diabetes mellitus, ASD-autism spectrum disorder, SLE-Systemic lupus erythematosus.

Regenerative stem cells and immunological diseases

Stem cell therapy research has thrown more light in the developmental, morphological, and physiological processes that govern tissue and organ formation, maintenance, and regeneration. The understanding of some of the stem cells can be translated into medical practice in the management of autoimmune disorders. Cellular differentiation, molecular processes, and tissue homeostasis are better appreciated

with new researches in stem cells. In Autologous stem cell transplantation (ASCT), mostly adult stem cells have been postulated for use in most common autoimmune disorders such as Systemic lupus erythematosus (SLE), Rheumatoid arthritis (RA), Multiple sclerosis (MS) and Sjogren syndrome (SS). There are more than 1000 cases of documented evidence of successful usage of ASCT in the treatment of autoimmune disorders. Stem cells can be used in the treatment of the immunological disease or the fixing of the damaged tissues or organs. This invariably means that there is no part of the approach to immunological diseases that stem cells cannot be applied. Documented facts proved that it is promising with a better outlook and side effects compared to the conventional management of these diseases.

In learning to live by the phrase "never say never in medicine", this indicates the possibilities and proven use of stem cells in many autoimmune conditions. In a few African tribes and amongst Chinese folklores, their practices have evidence of using placental tissue and Wharton jelly from the umbilical cord for the treatment of different diseases and use in spiritual practices for centuries. However, in the last decade, there is evidence to support the use of stem cells in orthodox medicine through evidence-based regenerative medicine.

Embryonic stem cells (ESCs) can be transplanted and transdifferentiated into more than 200 types of cells like retinal ganglion, hepatocytes, cardiomyocytes, pancreatic progenitors, chondrocytes, cones, egg sperm, and Sinoatrial pacemaker cells. The pluripotency fate of ESCs is governed by the functional dynamics of transcription factors OCT4, SOX2, and NANOG (Thomson J. A, 1998).

This diverse lineage commitment remains the main reason why ESCs can be used in many diseases. In spinal cord injury, it can be transplanted and noticeable improvement in balance, sensation, and movement are seen (Shroff G, 2015). ESCs can be used for age-related macular degeneration (ARMD) through genomic incorporation of the COCO gene during embryogenesis which can suppress TGFβ, BMP, and Wnt signaling pathways and allows commitment of ESCs into cone cells (Zhou S (2015). This allows ESCs to be used in the treatment and restoration of vision in ARMD and glaucoma patients. ESCs can also be used in cardiac cell regeneration by using

ESCs-derived cardiovascular progenitors, and bone marrow-derived mononuclear cells (BMDMNCs) but this is less effective than mature cardiomyocytes (Shiba Y 2012; Fernandes S 2015).

In liver pathology, ESCs can be used to regenerate the hepatocytes by adding ex-vivo VitK12 and lithocholic acid (a by-product of flora in the gut) which then activates pregnane X receptors (PXR), CYP3A4, and CYP2C9 and leads to conversion of ESCs into Cytochrome p450 hepatocytes. These hepatocytes also function in drug metabolism. This may be of utmost importance in autoimmune liver diseases, primary biliary cirrhosis/cholangitis (Avior Y, 2015).

Theoretically, diabetes mellitus can be cured using stem cells. Some models have demonstrated the generation of insulin-secreting β-cells marked with GLUT2, INS1, GCK, and PDX1 by PDX1 mediated epigenetic reprogramming or by transplanting stem cells positive for $CD24^+$, $CD49^+$, and $CD133^+$ and adding antidiabetic drugs as an enhancer (Bruin J. E, 2015; Salguero-Aranda C, 2016).

In arthritis, chondrocytes can be generated from ESCs, and transplanted chondrocytes (positive for SOX9 and collagen 11) form cell aggregates and can be active for 4 months making them effective for arthritis and cartilage lesions. In this model medical translation made be needed after more researches and trials are done (Cheng A, 2014).

The careful insertion and mixing of inert biomaterials like TBox3 and ESCs will generate sinoatrial nodes pacemaker cells which can be used in the treatment of a dying heart (Vedantham V, 2015). Tissue-specific progenitor stem cells (TSPSCs) retains stem cell plasticity and are relatively low in population, making harvesting somewhat difficult for therapeutic scale. Examples of TSPSCs with known possible therapeutic application are pancreatic progenitor cells (PPCs), dental pulp stem cells (DPSCs), inner ear stem cells (IESCs), intestinal progenitor cells (IPCs), limbal progenitor stem cells (LPSCs), epithelial progenitor stem cells (EPSCs), mesangioblasts (MABs), spermatogonial stem cells (SSCs), the skin-derived precursors (SKPs), and adipose-derived stem cells (AdSCs) (Greggio C, 2013).

PPCs require fibroblast growth factors and notch signaling to differentiate into insulin-secreting beta cells clusters which can be used in curing diabetes mellitus (Greggio C, 2013). DSPSCs which are known to transform neuronal cells express nestin, glial fibrillary acidic protein (GFAP), βIII-tubulin, and voltage-gated L-type Ca^{2+} channels. Expansion of DPSCs in chemically defined neuronal culture medium transforms them into a mixed population of cholinergic, GABAergic, and glutaminergic neurons; those are known to respond towards acetylcholine, GABA, and glutamine stimulations in vivo. This shows promise in neurocentral problems.

Encapsulation of mouse or human-derived MABs (engineered to express placental derived growth factor (PDGF)) into polyethylene glycol (PEG) fibrinogen hydrogel and their transplantation beneath the skin at ablated tibialis anterior form artificial muscles, which are functionally similar to those of normal tibialis anterior muscles. The PDGF attracts various cell types of vasculogenic and neurogenic potential to the site of transplantation, supporting transdifferentiation of mesangioblasts to become muscle fibrils (Fuoco C, 2015). The therapeutic application of MABs can be translated into the management of myositis/myopathy.

Mesenchymal stem cells/stroma cells (MSCs) are stem cells that differentiate into cells of mesodermal origin like tendons, bone, cartilage, ligaments, neurons, and muscles. Flow cytometric /immunocytochemistry shows combination of markers: $CD73^{+}$, $CD90^{+}$, $CD105^{+}$, $CD11b^{-}$, $CD14^{-}$, $CD19^{-}$, $CD34^{-}$, $CD45^{-}$, $CD79a^{-}$ and HLA-DR (Dominici M, 2006). The bone marrow-derived MSCs (BMDMSCs) from baboon with $CD105^{+}$, $CD73^{+}$, $CD34^{-}$, and $CD45^{-}$), expressing GFP reporter, coaxed with small intestinal submucosa (SIS) scaffolds, augment healing of degenerated bladder tissue within 10 weeks of the transplantation (Sharma A, 2011).

It is pertinent to note that MSCs have in-vivo chondrogenic, osteogenic, and adipogenic potentials. Treatment of MSCs with cytochalasin-D causes rapid transportation of G-actin, leading to an osteogenic transformation of MSCs, making it potentially useful in orthopedic and osteopathic medicine (Sen B, 2015).

Alopecia is caused by aging, medications, diseases like autoimmune conditions (SLE, autoimmune alopecia). GAG coatings made up of fibroblast growth factor 2 (FGF2) loaded alginate and gelatin, encased inside MSCs create tissue microenvironment for dermal papillae cells (DPCs) that can sustain immunological and mechanical obstacles, supporting the generation of hair follicle (Lin B.J, 2016).

Umbilical cord stem cells (UCSCs) possess enormous potential of rich hematopoietic stem cells (HSCs) and MSCs. It also has less ethical issues and non-invasiveness as compared to others because its routinely discarded in most of the world (Shahrokhi S, 2012). The proliferation of HSCs is regulated by Musashi-2 protein-mediated attenuation of Aryl hydrocarbon receptor (AHR) signaling in stem cells (Rentas S, 2016).

This is approved in the United States for treatment of immunological and hematological diseases though slower in utilization because of myriads of issues like concerns from patients, lack of consent, time-consuming in engrafting to maturity, risks of infection and mortality and diverse protocol (Mehta R. S, 2015).

Amniotic fluid stem cells (AFSCs), finely blended to fibrin, a protein required for coagulation/fibrinolytic pathway, ECM interactions, wound healing, and angiogenesis, hydrogel, and polyethylene glycol supplemented with vascular endothelial growth factor (VEGF), give rise to well-vascularized tissue (biocompatible tissue patches) for treating infants born with congenital heart defects in a model mice model (Benavides O. M, 2015). OCT4, KLF4, cMYC, and SOX2 transform into AFSCs into pluripotent cells called AFiPSCs by integrating them into a retrovirus. AFiPSCs, then differentiate into extraembryonic trophoblast by BMP2/4 to regenerate placenta and therefore may be important in autoimmune placenta disorder like pre-eclampsia and eclampsia (Wolfrum K, 2010).

Wharton's jelly (WJ), a mucopolysaccharides rich gelatinous materials from the umbilical cord made up of fibroblasts, macrophages, and stem cells. Transplantation of WJ-SCs to streptozotocin-induced mice reduces the blood sugar to normal because it can transdifferentiate into β-cells. WJ-MSCS with CD34 + has the best regenerative potential with fewer chances of host versus graft reaction. StemRegenin-1 added may further expand the clonal expansion of CD34+ (Leferink A. M, 2015; Wagner J. E, 2016).

In diabetic mellitus, a trial of WJ-MSCS demonstrated restoration of pancreatic function, enhanced c-peptides, and reduction in IL-6 and IL-1*β and T-cells. (*Liu X., Zheng P., Wang X, 2014). *Likewise, in systemic lupus erythematosus(SLE) it was shown to decrease the morbidity in 40 patients model, decreasing* systematic lupus erythematosus disease activity index (SLEDAI) and British Isles Lupus Assessment Group (BILAG). (Wang D (2014). This can also be used in a different model to treat neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, stroke, Krabbe's disease, hurler syndrome, adrenoleukodystrophy (ALD), metachromatic leukodystrophy (MLD), Tay-Sachs disease (TSD) and Sandhoff disease. UCSCs can induce angiogenesis, reduce scarification, and improves cardiac function in pigs, thus it can be promising in myocardial infarction, aging, host inflammation (Chang M.Y, 2016).

Bone marrow stem cells (BMSCs)are derived directly from the bone marrow. The bone marrow is sandwich between bones and red marrow which produces myeloid series like red blood cells, platelets, and granulocytes, while the yellow marrow produces fat cells and some white blood cells. It produces all the peripheral blood and hemopoietic stem cells (Travlos G. S, 2006). BMSCs can be modulated in the prevention of HIV, treatment of diabetic mellitus, multiple sclerosis, dental caries, and liver disease from hepatitis C. A single dose of a clone of BMSCs in mice can restore erectile function in diabetic mice (Morizane R, 2015).

Infection with HIV-1 is mediated through $CD4^+$ receptors, chemokine CXC motif receptor 4 (CXCR4), and CCR2 chemokine receptor 5 (CCR5) for infecting and propagating into T helper (Th), CCR2, monocytes, macrophages, and dendritic cells (DCs) in humans, making it impossible to treat with BMSCs. The only way to genetically modify the CD4+ cells from the stem cells to express HIV 1 specific RNA antagonistic RNA to eliminate the infected CD4+.Administration of a single dose of such genetically modified stem cells can be an alternative to anti-retroviral drugs. The downside to this will be patient selection, transplantation conditioning regimen (chemotherapy usage), and post-infusion follow up studies may be the major issues in this scenario (DiGiusto D. L, 2013; Herrera-Carrillo E, 2015).

BMSCs can transdifferentiate into brain cells in case of brain injuries like stroke, multiple sclerosis, and others. In diabetes mellitus and multiple sclerosis neuropathy, lipoic acid is combined with BMSCs to induce angiogenesis and increased blood flow to the brain, which subsequent conversion of the stem cells to brain tissue and recruitment of microglia to form scaffold between 8 to 16 weeks (Paradells S, 2015).

In degenerative liver disease secondary to hepatitis C infusion, intravenous infusion of intraparenchymal transplantation of bone marrow mononuclear cells (BMMNCs) lowers serum level aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin, CD34, and α-SMA, suggesting the restoration of hepatic functions through the regeneration of hepatic tissues by infused BMSCs (Lukashyk S. P, 2014).

In the nearest future, the use of induced pluripotent stem cells (iPSCs) will be welcomed fully in the management of complications of immunological diseases. This is becoming an acceptable stem cell therapy because it can be easily generated from adult somatic cells using specific transcription factors called Yamanaka's factors coded on specific genes like cMYC gene, Oct3/4 gene, Sox2 gene and Klf4 gene incorporated into skin fibroblast (Takahashi K, 2006). They can regenerate several organs like liver, neurons, heart, pancreas, and red blood cells. iPSCs can be used in regenerating loss cells in Alzheimer's disease, kidney injury, ARMD, schizophrenia, infection like HIV, bipolar disorder, and other neuropathological conditions, genetic and acquired seizure disorders, fixing and correcting genetic mutation by removing unwanted epigenetic (Howden S. E, 2015; Mahla R. S, 2016). It is known that α-1 antitrypsin deficiency (A1AD) is caused by single base pair mutation and correction of this mutation fixes the A1AD deficiency in hepatic-iPSCs (Wilson A. A, 2015).

Diabetes mellitus can be treated with a model of reprogramming skin cells to pancreatic cells, bypassing the pluripotency phase, which can yield clinical β-cells. It's safe and effective reprogramming in stem cells and can be used in curing diabetes mellitus. The process involves the transformation of skin cells into definitive endodermal progenitors (cDE) and foregut like progenitor cells (cPF) intermediates and subsequent in vitro expansion of these intermediates to become pancreatic β-cells (cPB). This reprogramming is

supported by pluripotent factors (OCT4, SOX2, KLF4, and hairpin RNA against p53) on day 1 and by day 7 and 14 growth factors and chemicals are supplemented (GF, b-FGF, CHIR, NECA, NaB, Par, and RG, Activin-A) (Zhu S., Russ H. A., Wang X, 2016).

Stem cell medicine proffers theoretical solutions to lots of medical conditions but most importantly ethical issues remain the main concern in its use except for umbilical cord stem cells. The excellent advancement in recent years in stem cell research is promising, projecting the ability to produce a wide array of tissue, organoid, and organs from adult stem cells. Inductions of pluripotency stem cells in terminally differentiated adult cells have a better therapeutic future than ESCs, due to least ethical concerns with adult cells. In other to optimize the advancement of translational application of stem cells, there is a need for more clinical trials, which needs funding rejoinder from both public and private organizations. The need to achieve success and efficacy of stem cell translation within a good time frame, explains why we must evaluate the regulatory guidelines for all stages of clinical trials (Mahla R. S, 2016). Extract from major successfully and potential novel use of stem cells in the treatment of common immunological diseases are summarized below highlighting different perspectives of the treatment from procedural, limitations, and others.

Stem cell transplantation can destroy the defective immune system, renew the lymphatic system and angiogenesis, reduce the disease activity, and lead to long-term remission with reasonable and appreciable immunomodulatory and immunosuppressive capability in lots of autoimmune disorders. This is evident by patients with immunological disorders who were once resistant to conventional therapy, following transplantation, have become sensitive to the same conventional therapy, highlighting the immunomodulatory properties of stem cell transplantation.

Most clinical studies based on stem cell therapy in immunological disorders are using autologous hemopoietic stem cell therapy from bone marrow to peripheral blood. There is practically no significant difference in the transplantation protocols used for different diseases. The results shown in this review range from cases of complete or partial remission, relapse, or stabilization of disease to cases involving the advancement of the disease and death. Patient selection, techniques, use of chemotherapy, source of stem cell, locations appears to

directly influence the results of transplantation. It is safer and more effective to choose patients in the initial stages of the disease because generally the outcome and almost near remission is seen. However, this procedure involves the risk of exposing patients who may respond well to conventional therapy to new non-standard treatment methods. It should be pointed out that most of the procedures reviewed here were performed in patients that failed to respond to conventional treatment therapies. In such patients, the use of stem cells, although still being an experimental procedure, provides a new chance to enhance the quality of life.

There are some controversies highlighted in the use of stem cell therapy and one of the important ones is regarding the use of a high dose of chemotherapy in the absence of stem cell infusion, which, in some cases, has led to satisfactory results, suggesting that immunosuppression may be the real cause of the improvement seen in the patients, and not the stem cells transplantation by itself.

Another area of concern in stem cell therapy is the small sample size since they represent case reports and small uncontrolled case series especially for Brazil and the United Kingdom. Also, the individuals represent highly diverse genetic backgrounds, and only randomized clinical trials following standard procedures will allow us to reach meaningful conclusions. Furthermore, there is a need for studies that will evaluate the use of maintenance therapies after transplantation, define patient selection protocols, and assess stem cell mobilization in the treatment of autoimmune diseases. We have to remember infection control too pre-, intra-and post-transplantation, though it is not as significant as alloimmunity, graft vs host disease, and relapse.

It is generally observed in an autoimmune disease that about 30% will have a relapse following autologous stem cell transplantation while 5% of allogeneic transplantation develop relapse. The result of allogeneic transplantation is generally favorable and tends to produce a better quality of life. Relapse could be caused by contamination of the graft with autoimmune cells can which we can be contained by using pure cell lines expanded in the laboratory, which would also increase the number of stem cells available for the patient, the incapacity of the conditioning regime to destroy the immune cells responsible for the disease or the presence of the defect in the stem cell expansion. The efficacy of allogeneic transplantation is mainly the result of the change in the genetic susceptibility of

the host to the disease, and also involves the graft-versus-disease effect. Currently, this procedure is not frequently used due to its toxicity and the need for HLA compatibility.

The use of mesenchymal stem cells represents a promising therapy for autoimmune disease, because they tend to have more immunosuppressive properties and reports are suggesting the low level of expression of HLA molecules, thus less likely to have graft versus host disease. It is believed that the therapy mediated by mesenchymal cells may permit the secretion of immunosuppressing factors and may repair the tissue destroyed by the chronic inflammatory process.

In neurodegenerative diseases, stem cell therapy is showing lots of promises because neural stem cells may remain in the quiescent stage due to the unfavorable microenvironment caused by disease, and It is believed that genetically modified stem cells can stimulate the proliferation of endogenous stem cells and that may lead to repair of the damaged neural region as in research trials of Amyotrophic lateral sclerosis, but this is not discussed in this forum because it is not distinctly categorized as an autoimmune disease.

Stem cell-based therapy offers the possibility of developing new treatments in many cases of autoimmune disorders with several reports having analyzed the potential benefits of stem cell transplantation in these diseases. It is hoped that new studies currently underway will show good results for the treatment in the near future.

Stem cell therapy in autoimmune disease is showing lots of promises and demonstrated better efficacy and lesser side effects than conventional therapy. In most of the reviews, it has shown relatively high immunomodulatory effects in therapy-resistant patients. The use of stem cells is still in the infantile stage, but demonstrating high chances of a positive response by patients despite small patients' size and uncontrolled series. We hope in the future more research can be done with individuals with diverse genetic backgrounds and only randomized clinical trials following standard procedures will allow further research work to achieve a curative level for all immunological diseases.

It is generally observed that relapse occurs in about 30% of autologous transplantation while 5% in allogeneic, with allogeneic having a better prognosis because of the change in genetic susceptibility and graft versus host effect (Fassas A, 2003) Allogeneic transplantation not being used because of the HLA compatibility and toxicity.

ESCs is a good stem cell to use because it is less immunogenic and has greater transdifferentiation capability, but the use is limited for ethical reasons and can transform to teratoma. ASCs has a high risk of rejection as compared to ESCs. MSCs are also showing lots of promises, especially for neurodegenerative diseases. It is observed in most trials to have immunomodulatory effects and may fix damaged tissues (Rosa SB, 2007).

Rheumatoid arthritis (RA) and Juvenile idiopathic arthritis (JIA)

Rheumatoid arthritis is a multisystemic autoimmune disorder that, in the long term, can lead to irreversible destruction of the joints, ligaments, and tendons (Enthesis) leading to loss of mobility, as well as a reduction in both the quality of life and life expectancy. Abnormal cellular and humoral immune responses can contribute to the development of multisystemic lesions. Rheumatoid factor, an autoantibody (IgM) whose Fab region is specific to the Fc region of human IgG, is produced in more than 80% of patients with Rheumatoid arthritis and pivotal to the development of various manifestations of Rheumatoid arthritis. Another antibody worth mentioning is an anticitrullinated peptide found in most joints. The deposition of immune complex (Type 3 hypersensitivity reaction) in the tissues mostly small joints, lungs, heart, and soft tissues initiates complement activation and recruitment of inflammatory cells like macrophages, plasma cells and T-cells with subsequent production of cytokines like IL-1, IL-6, and TNF-alfa leading to panniculitis and destruction of the tissue. The inflammatory cells, cytokines, and antibodies are the target for the treatment of the disease with suboptimal responses and complications in most cases, reasons why there is a need for introduction of stem cell treatment as a major substitute and, or as an adjuvant (Ringe J, 2009).

The inflammatory cells involved in Rheumatoid arthritis are predominantly derived from hemopoietic stem cells, which suggests that this disease may originate from problems in stem cells, but not sure if it’s normal or abnormal stem cells derivative. Allogeneic stem

cell transplantation can cure RA in most cases, this proved beyond doubt that the pathology originates likely from stem cell defects or aging stem cells.

In RA, the abnormal functioning of stem cells is probably not limited to HSCs, but may also involve, for example, MSCs. Thus, the premature aging of stem cells in RA may lead to tissue destruction resulting from the action of T-cells and failure of the tolerance mechanism. Environmental factors like cigarette smoking and silica are associated with tissue injury and accelerated aging of cells especially T-cells. The T-cells express distinct immunoregulatory receptors that potentiate the HLA-DR4 allotype activity presents in hemopoietic stem cells and possibly mesenchymal stem cells, independent of antigenic recognition, leading to pro-inflammatory and auto-reactivity with wanton destruction of tissues. The conventional management of RA involves the use of analgesic (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) like methotrexate, hydroxychloroquine, or intra-articular corticosteroid injections with a remission rate of only 15% (Hayward K, 2009).

Autologous hemopoietic stem cell therapy (AHSCT) is the most commonly adopted more than syngeneic or allogeneic bone marrow transplantation. The usage started in the 80s with animal models but now done on human models, and now available for treatment in few centers around the world. The technique involves stimulation and mobilization of granulocyte colony-stimulating factor(G-CSF) before leukapheresis, while the donor may or may not be immunosuppressed with cyclophosphamide. Antithymocyte globulin (ATG) may be used in the treatment of the graft in vivo or ex vivo or selection of CD 34+cells. The rationale is to reduce or eliminate mature autoreactive lymphocytes, which may cause tissue injury (Figure 3) (Moore J, 2002).

The recipient is subsequently subjected to adequate and intense immunosuppression using cyclophosphamide following the reintroduction of stem cells. The cyclophosphamides increase stem cell quality and quantity, reduce reactive T cells, stimulate the production of immunocompetent cells, and reestablished immunological balance, overall reducing the chances of carrying out the

procedure all over again. It is believed to be the best form of treatment in drug-resistant Rheumatoid arthritis (Moore J, 2002; Verburg RJ, 2001).

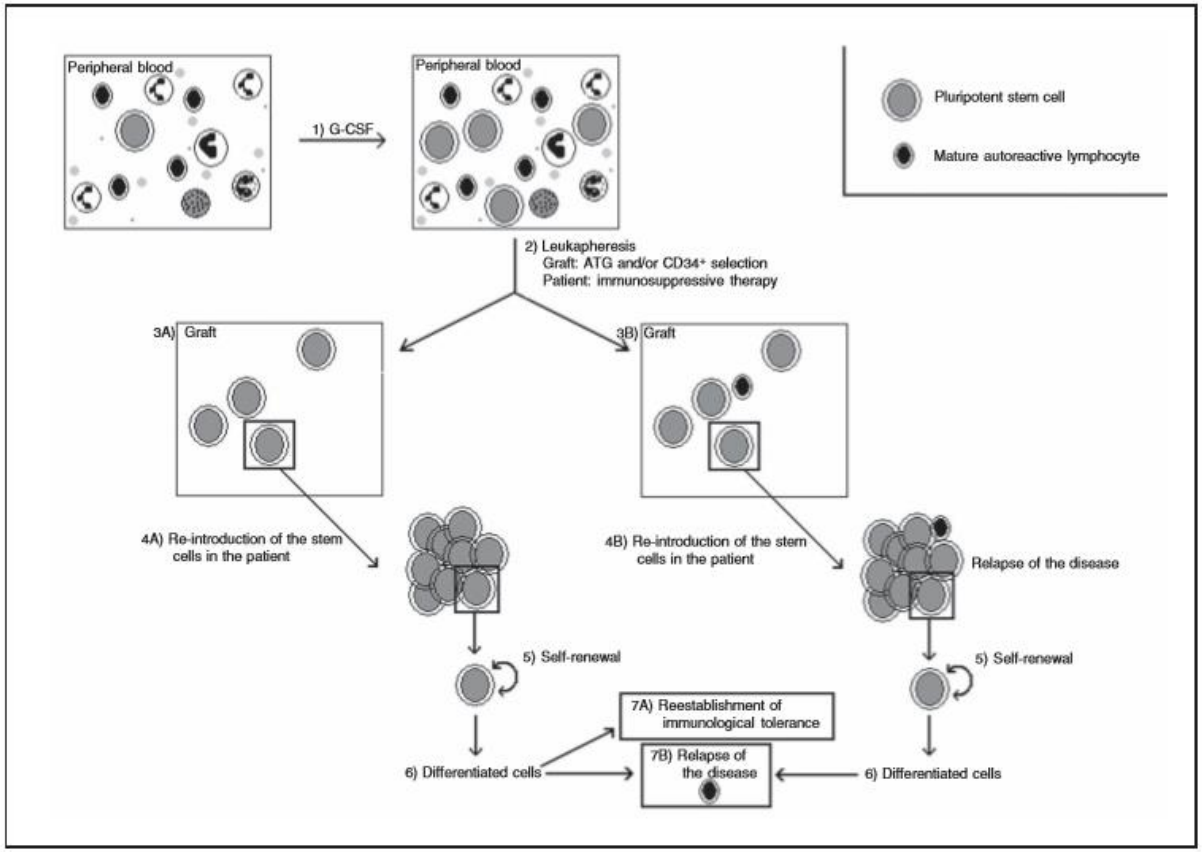


Figure 2.3

The European Group for Blood and Marrow Transplantation (EBMT) and the Autologous Blood and Marrow Transplant Registry, involved the collection of results from around the world of 76 cases of treatment of RA with stem cells, particularly those with severe and resistant cases from 1996 to 2000. It was documented that there was an outstanding response to stem cell treatment with 1 death but

high rate of relapse. There was a better response to the usage of conventional antirheumatic drugs following stem cell treatment, which supports the role of stem cell therapy in immunomodulation. In the study, though not cured with autologous HSCT, it is safe with 50% of ACR 50 or better response after 12months than DMARDs with only a 15% response rate (Snowden JA, 2004; Jayne D, 2004; Burt RK, 2006).

In a study by (Moore et al., 2006), of more than 33 patients, adequate inference that stem cell transplantation among twins results in better treatment response. Hemopoietic stem cell therapy in Rheumatoid Arthritis therapy is well tolerated by patients, with few cases of deaths, though stem cell therapy is not considered to be a curative therapy for Rheumatoid arthritis. In the studies, the laboratory established the role and advantages of hemopoietic stem cells, stromal stems and create a database on which subsequent research work stem cells in clinical translation are based. (Moore KA, 2006)

Systemic JIA is a heterogeneous form of arthritis in childhood and represents more than 10% of all cases of JIA in the Caucasian populations of Northern America and Europe with poor response to therapy especially anti-TNF agents, thus has high mortality and morbidity with more than 30% with the active disease after 10 years despite chemotherapy.

In the last 2 decades of the trial of 50 children with refractory JIA, the idea of stem cell therapy is the same as for Rheumatoid arthritis but there are documented and procedural differences among the south America group and the European group. The European Bone Marrow Transplantation Group is mostly using and plans to continue using adult stem cell therapy in the treatment of JIA, particularly the systemic onset form of the disease adopting fludarabine in the conditioning regimen. The stem cell treatment carries a high mortality, though recent studies show reduction with the addition of pre-treatment steroids. Retrospective studies of children treated with this technique show a total of 34 children received adult stem cell therapy, 53% earlier treated with anti-TNF had complete drug free remission for 12 to 60months,18 % had partial recovery ranging from 30% to 70%, 9% treatment-related mortality and 6% disease-related mortality. In another study, Endothelial progenitor cells (EPCs) with methotrexate were used on 51 children, the results show a

significant increase of circulating progenitor stems cells and demonstrable vasculo-protective and repairing ability of EPCs. Trials by Brinkman et al., 2007 on 22 patients with refractory JIA showed complete remission in 15 patients on ASCT on an average of 80 months therapy, with 2 deaths from macrophage activation syndrome. 5 patients had a relapse, 7 were partial responders and 8 out of 20 patients had reached complete clinical remission. A modification is done with antiviral medications and steroids subsequently, and there was not a single ASCT associated death reported (Martini, 2015; Brinkman DM, 2007).

The Brazilian Cooperative Trial of Autologous Hematopoietic Stem Cell Transplantation for autoimmune disease had only one patient, a 20-year-old female patient with the polyarticular form of JIA. She was given Cyclophosphamide for immunosuppression and immunomodulation, rabbit antithyroid globulin (ATG), and autologous peripheral blood stem cells. Anti-CD20 monoclonal antibody (Rituximab) was given for 3 months to prevent relapse and the patient maintains complete remission after 1 year of follow-up (Rosa S.B et al., 2007).

Diabetes mellitus

It will be inconclusive without looking at the recent stem cell treatment of one of the world-leading causes of morbidity, co-morbidity, and mortality. Diabetes can comfortably be tagged as a pandemic, sparing no race, gender, or country affecting approximately 6-8% of the world population and the number of newly diagnosed patients increases yearly. Approximately 10% of all diabetes mellitus is type I diabetes(auto-immune), which is insulin-dependent diabetes mellitus. In recent studies, there is evidence that suggests that the disease could be cured if an adequate supply of new ß-cells (cells in the pancreas that produce insulin) were made available. The aim is to understand and perfect through developmental regeneration biology, how to produce the pancreatic ß-cells exogenously using various clinical trials of the stem cell production of ß-cells.

There is no doubt that pancreatic islet cell transplantation is an excellent treatment of type I diabetes. Clinical islet transplantation trials based on cadaveric allogeneic islets have demonstrated that it is indeed possible to restore near-physiological insulin secretion capacity

in type I diabetic patients through transplantation of insulin-producing cells. There are several difficulties associated with islet allogeneic transplantation such as problems related to alloimmunity, autoimmunity, and the need to secure large quantity islet cells.

A very good alternative is securing an adequate quantity of islet cells for transplantation is harvesting from animals because of shortage and the complicity in harvesting from humans, but this is a burden with the risk of infection from animal endogenous islet cells and lifelong post-transplantation immunosuppressant thus limiting its usage.

It is established from recent researches and studies on stem cells that bone marrow contains hemopoietic stem cells and mesenchymal cells that are known to have the capability of differentiating into several different kinds of cells such as pancreatic ß-cells, but it is laced with lots of controversy and issue such as inability to retain full functionality. Experimental transplant models with insulin-producing cells in animals have demonstrated reversal of diabetes and near-normal state in which production and release of insulin and prolonging the life of the animal (mice were used in the study).

Researches have demonstrated the potential use of primary cultures of adult human liver cells as pancreatic progenitors, showing the potentials of liver cells. The use of pancreatic progenitor tissue has been demonstrated both *in vivo* and *in vitro* in *Xenopus* mice and humans. The use of adult human liver cells for generating functional insulin-producing tissue may pave the way to autologous implantations, thus allowing the diabetic patient to be the donor of his or her insulin-producing tissue. This will markedly reduce the risk of rejections (graft vs host disease, failure of engraftment) and lifelong use of immunosuppressants which comes with its complications. Bone marrow stem cell transplant can produce chimerism which can affect type 1 diabetes mellitus in several ways like inducing tolerance to pancreas and islet cell transplants, and secondly by reversing the autoimmune process before the development of terminal complications. In a way, it can be used to the advantage of the patient if properly done resulting in a better quality of life but the morbidity and mortality associated with lethal conditioning could not be justified for tolerance induction or interruption of the autoimmune state in type I diabetes. While immune destruction of the pancreas can pose a major problem in bone marrow

transplantation, a new approach with splenic mesenchymal cells has yielded promising results in both pancreatic ß-cell regeneration and immune destruction prevention. Though significant advances have occurred in the treatment of type I diabetes during the past century, bone marrow and possible splenic mesenchymal cell transplantation are the only methods capable of interrupting and reversing the autoimmune process before the development of terminal complications, the earlier more applicable. Among the multiple genes implicated in susceptibility (and resistance) to T1D, the most important is the human leukocyte antigen (HLA) complex on chromosome 6, in particular the HLA class II. Two susceptibility haplotypes in the HLA class II region are now considered the principal susceptibility markers for T1D. Although 90–95% of young children with T1D carry either or both susceptibility haplotypes, approximately 5% or fewer persons with HLA-conferred genetic susceptibility actually develop clinical disease (Mehers et al., 2008; Virtamen et al., 2003).

Approximately 40–50% of familial clustering in T1D is attributable to allelic variation in the HLA region. The remaining genetic risk is made up of many diverse genes, each having a small individual impact on genetic susceptibility. A number of reports suggest a recent temporal trend of fewer high-risk HLA genotypes in youth diagnosed with T1D, suggesting an increased influence of environmental factors in the development of T1D during the past few decades (Mehers et al., 2008; Concannon et al., 2005; Vehik et al., 2008; Hermann et al., 2003). Although the majority of T1D cases occur in individuals without a family history of the disease, T1D is strongly influenced by genetic factors. In the United States, individuals with a first-degree relative with T1D have a 1 in 20-lifetime risk of developing T1D, compared to a 1 in 300-lifetime risk for the general population. Monozygotic twins have a concordance rate of > 60% if followed long enough whereas dizygotic twins have a concordance rate of 6% to 10%. Genetic susceptibility for T1D ranges from marked in childhood-onset T1D to a more modest effect in adult-onset T1D, with children having a higher identical twin concordance rate and a greater frequency of HLA genetic susceptibility (Rendondo et al., 2001; Rendondo et al., 2008; Rendondo et al., 2001; Fourlanos et al., 2005). Siblings of children with onset of T1D before the age of 5 years have a three- to five-fold greater cumulative risk of diabetes by age 20 compared to siblings of children diagnosed between 5 and 15 years of age. Diabetes with onset before age 5 years is a marker of high familial risk and suggests a major role for genetic factors. The offspring of affected mothers have a 2% to 3% risk, whereas offspring of affected fathers have a 7% risk. An association between T1D and other autoimmune diseases, such as autoimmune thyroid disease,

Addison's disease, celiac disease, and autoimmune gastritis, is well established. The clustering of these autoimmune diseases is related to genes within the major histocompatibility complex (Gillespie et al., 2002; Hamalainen et al., 2002; Tsirogianni et al., 2009; Barker et al., 2006).

In the nearest future when the techniques and various sources of stem cells are better understood and perfected, we hope the limitations and complications associated with bone marrow transplant are overcome, and it becomes fully a therapeutic option in the treatment of autoimmune diabetes and tolerance induction.

University Hospital of the School of Medicine of Ribeirão Preto, Brazil trials on 15 patients with early-onset type 1 diabetes from December 2003 to July 2006 less than 6 weeks from diagnosis were given autologous hemopoietic stem cell with cyclophosphamides (200 mg/kg) and rabbit ATG (4.5 mg/kg) as a conditioning regime. 14 patients without previous ketoacidosis and steroids for conditioning, 86% became insulin-free shortly after transplantation, 13% after 1 year from transplantation, and 7% patient relapsed after a viral infection. (Rosa SB.,2007)

Systemic lupus erythematosus (SLE)

SLE is multi-systemic autoimmune disease-causing multiple organ/tissue damage. It is a type 3 hypersensitivity reaction in which the body's immune system attacks healthy tissue by deposition of immune complexes in various parts of the body with subsequent complement activation and tissue damage. It is mostly seen among Africans and African American women within ages 20 to 35. The etiology of SLE is not known, but it could be linked to some genetic factors, hormonal factors, environmental factors like medications such as hydralazine, quinidine, sulphonamides, isoniazid, and procainamide. The long-term use of the above drugs causes SLE-like symptoms mostly seen in slow acetylators. (Robbin et.al., 2004; Warren et.al., 2020).

The disorder is diagnosed using the American society of rheumatology criteria based on 4 or more of the clinical findings. The findings in SLE are rash (malar or discoid), arthritis, mucosal ulcers, hematologic manifestations(pancytopenia), photosensitivity, renal disease (Nephritic syndrome), Neurologic disorders (depression, mood liability), serositis (Pericarditis, pleuritis, peritonitis). A number Blood tests can also be used for diagnosing SLE such as Anti-nuclear antibody (ANA) test, Anti-double-stranded DNA (anti-dsDNA) antibody, Anti smith antibody (most specific test), antiphospholipid antibody test (anti-cardiolipin and lupus anticoagulant) which is associated with recurrent abortion, anti-histone antibody (for drug-induced SLE), Anti-Ro(SSA) associated with intrauterine fetal heart block and Anti-La(SS-B), Low serum complement level(examples, C1q, C4, C2), false-positive VDRL, elevated erythrocyte sedimentation rate, kidney, and liver function tests and complete blood count. These tests can also help monitor disease progression after diagnosing and treatment of the condition. (Robbin et.al., 2004; Warren et.al., 2020)

There is no cure presently but the condition responds very well to some medications if the diagnosis is made early and treatment is instituted, with good compliance. Example of classes of drugs generally used are;

- Non-steroidal anti-inflammatory: used for joint pain and stiffness and reduces inflammation
- Steroid cream: can be used for rashes
- Antimalarials (hydroxychloroquine): it is used to reduce inflammation, for skin rash, treatment of fatigue and joint pain, and control kidney disease
- Steroid tablets: used for complications such as pleurisy or pericarditis
- Disease-modifying anti-rheumatic drugs: examples azathioprine, cyclophosphamide, methotrexate, and mycophenolate.
- Biological (monoclonal antibodies) therapies: examples are Rituximab and Belimumab.

The untreated and resistant condition can progress to renal failure, cerebrovascular accident, vasculitis, seizures, or cardiovascular accident. The next level in attaining cure for SLE is stemming towards stem cell therapy because most patients with this disease often

present with Bone marrow dysfunction and a significant decrease in numbers of $CD34^+$ cells and a possible reduction in stem cell proliferation capability. The patients presented with increased levels of programmed cell death in the $CD34^+$ cell and a reduction in colony-forming units when compared to control groups. After bone marrow transplantation, it was observed that there is a significant reduction in programmed cell death of CD34+ cells when compared to the start of treatment. (Jayne D, 2004; Burt RK, 2006).

Between 1995 and 2002, the European Society for Bone Marrow Transplantation and the European league against Rheumatism registered fifty-three cases associated with the use of Hematopoietic Stem Cell Transplant (HSCT) in patients with SLE. In the United States, a transplant center also reported the use of HSCT in 50 cases from 1997 to 2005. Presently, a combination of Cyclophosphamide and G-CSF is used for mobilization, and high doses of Cyclosporin combined with Anti-thymocyte globulin (ATG) and *in vitro* $CD34^+$ cell selection. Besides the SLE patients submitted to HSCT and the American studies, 32 other isolated cases have been reported, with 68.75% of the patient having clinical remission. About 30% of the patients who had remission of the disease presented a relapse. (Rosa SB 2007, Jayne D, 2004; Burt RK, 2006). It was observed that the longer the post-transplantation period, the greater the risk of relapse, which is associated with a low level of anti-dsDNA antibodies prior to HSCT. According to the EBMT/EULAR studies, there was no difference in the frequency of relapse with selection of $CD34^+$ cells or with a more intense conditioning regime. The side effects of the treatment are not severe and the activity of the disease can be controlled with therapies. (Rosa S.B, 2007)

There are several instances of clinical improvement in patients with SLE treated with high doses of Cyclophosphamide. However, new inflammatory and autoimmune processes have occurred in patients submitted to HSCT and in patients treated only with Cyclophosphamide without the infusion of stem cells. This most likely occurred as the result of the deletion of regulatory T cells.

The first four cases of SLE in Brazil submitted to Autologous Hematopoietic Stem Cell Transplant were reported in 2003. Cyclophosphamide and Anti-thymocyte Globulin were administrated to patients at high doses before and after the stem cell transfusion. The use of ATG immediately after the infusion was designed to complement the *in vivo* T cell deletion since in the protocol, the infused

cells did not suffer *in vitro* selection. Three patients presented with severe kidney failure and 1 patient died. The three surviving patients showed remission of kidney disease after transplantation, but 1 patient relapsed thereafter and showed a decline in renal function. Four other patients were included in the clinical trial, 1 patient could not have his stem cells mobilized and returned to conventional immunosuppression and 3 patients died from transplantation related complications (Voltarelli, 2005; Rosa S.B, 2007)

There are quite a number of international literatures proving that AHSCT is efficient in achieving remission of disease in patients with resistant SLE. Transplantation can change the behavior of severe diseases, making them more benign and responsive to therapy. It has been suggested that the reported higher rates of mortality in Brazil and other countries can be controlled by appropriate patient selection, the choice of a less aggressive conditioning regime, and the acquisition of more experience in managing specific complications associated with the procedure. (Rosa S.B,2007)

Multiple sclerosis (MS)

Multiple sclerosis is an autoimmune demyelinating disease of the brain and spinal cord whereby the T cells of the immune system attack the myelin leading to axonal damage and sclerosis. This eventually causes slow or disrupted electrical transmission through the neural tissues. It is most commonly diagnosed in patients in their 20s and 40s, also it is more common in women than men in the temperate region. Most patient with MS is diagnosed with relapsing and remitting type of MS, while the rest would have a gradual progression or worsening of symptoms. It is a lifelong condition that can cause serious liability. The cause is not known yet but a combination of factors such as genetic susceptibility, viral infections though not confirmed (Herpes viruses, rubella, measles, mumps), abnormalities in the immune system and environmental factors (cigarette smoking, stress, toxins, vaccines, hormones) could trigger the disease process. (Robbin et.al., 2004; Warren et.al., 2020).

It is autoantibodies (IgG) against oligodendrocytes (central nervous system) mediated major histocompatibility complex (MHC) class 2 defined as human leukocyte antigen (HLA) DR15 and DQ6. Diagnosis can be made using McDonald's criteria using clinical, laboratory

tests and radiological evidence of lesions in different times and space. The clinical manifestations discussed below with non-contrast MRI (with Gadolinium) showing plaques and lumbar tap cerebrospinal fluid showing pleiocytosis and IgG oligoclonal band are of great value. Signs and symptoms of multiple sclerosis may vary from person to person depending on the amount of neural damage. (Robbin et.al., 2004)

Symptom may include;

- Partial or complete loss of vision (optic neuritis), blurry vision, diplopia, nystagmus/ internuclear ophthalmoplegia.
- Numbness or weakness of one or more limbs, pain, hypoesthesias, paraesthesias, and muscle spasm.
- Intention tremor, ataxia, Scanning speech (Charcot triad).
- An electric shock-like sensation that occurs around the cervical spine with neck flexion and may radiate to your arms and legs (Lhermitte sign).
- Tingling sensation or pain in parts of the body.
- Fatigue, cognitive impairment, depression, anxiety, unstable mood.
- Bowel and bladder incontinence.
- Worsening of symptoms due to exposure to high temperature, a concept called Uhthoff's phenomenon.

There is no single test for diagnosing MS, rather a diagnosis is concluded by ruling out other conditions that have similar symptoms. Diagnosis might begin with a medical history and physical examination. Other recommended tests could include; MRI, spinal taps/ lumbar puncture, blood test. There is no cure for MS. Treatment generally focuses on halting progression, speeding up recovery, and managing its various symptoms.

- Treatment for acute flare: corticosteroid, plasma exchange(plasmapheresis)

- Treatment to slow progression and reduce relapses: Disease-Modifying Therapy (DMT) such as ocrelizumab, injectables interferon beta, and monoclonal antibodies (such as glatiramer, natalizumab), oral medications (examples include fingolimod, diethyl fumarate, teriflunomide and infusion medication (such as alemtuzumab and mitoxantrone).
- Treatment of major signs and symptoms: physical therapy, muscle relaxants for muscle stiffness or spasticity, medication to increase speed (dalfampridine), catheterization for neurogenic bladder.
- Other medications could be prescribed for pain, bladder and bowel incontinence, sexual dysfunction, and depression.

As mentioned earlier, the treatments highlighted for multiple sclerosis are not curative. They can reduce inflammation in the CNS and delay the progression of the disease, but disease control is still not satisfactory. Stem cells can be used in the treatment of MS because of the immunosuppressive effects of Autologous Hematopoietic Stem Cell Transplant (AHSCT), this may help balance the immune system. Because MS affects several parts of the brain and spinal cord, it makes the injection of stem cells into each infected site difficult to achieve. Therefore, intravenous injection of the stem cell could be the next option in MS and other conditions with neuroinflammation, in which there is the permeation of blood-brain barrier in the inflammatory areas. Also, the findings that stem cells can reach the CNS and differentiating oligodendrocyte, could propose that re-myelinization and neuronal repair is ultimately possible.

In 1995, the first case of stem cell transplant in patients with multiple sclerosis was carried out. As of November 2002, MS had the greatest number of stem cell transplant when compared to other autoimmune diseases. 200 patients were recruited for stem cell transplant in Multiple sclerosis. Almost all the patients were in the progressive phase of multiple sclerosis. These patients had not responded to treatments and have severe functional incapacity. Stem cell transplant reduced the inflammation to a greater extent in the CNS and enhanced the results obtained with conventional therapies. One of the major side effects was that infection occurred and this affected a huge percentage of the patient involved in the clinical trials. The death rate associated with the stem cell transplant was about ten percent which was high when compared to the death rate of the regular drugs. There is a probability that with a more accurate selection of patients, the death rate could be minimized. The deaths in stem cell administration could be linked to the severity of T-cell deletion,

advanced age of the patient affected and /or the level functional capacity loss in the selected patients. Some studies have proved that there is still a failure of resolution of cerebral atrophy after stem cell transplant for Multiple sclerosis but, it is still not certain if the stem cell was the cause of the atrophy judging from the patient's presentation with rapidly progressing form of multiple sclerosis which might lead to atrophy occurring at a faster pace. There is also a probability that the atrophy could be due to the fact that the disease had occurred previously. These are all postulations and more works still needed to done to ascertain these facts. (Fassas A.2002, Fassas A. and Passweg JR 2002)

Autologous Hematopoietic Stem Cell Transplant (AHSCT) does not produce good results in patients whose disease progression include degeneration of axon. Therefore, using AHSCT in the early stages of this disease would appear to be more suitable for patients with a decreased level of functional incapacity.

Matrix metalloproteinase-9 (MMP-9), a marker of MS pathogenesis, is regulated by the tissue inhibitor of MMP-1. The serum and expression level of mRNA of MMP-9 and tissue inhibitor of MMP-1 were analyzed in peripheral mononuclear cells from 14 patients with MS after AHSCT. The results indicated inhibition of MMP-9 activity, which is in accordance with clinical condition and reduction of disease activity. (Bianco Y.2004)

The process by which stem cell transplant affects the advancement of MS is not yet established. The immediate effect appears to be the elimination of autoreactive clones. The selected patients treated with stem cell transplant show a decrease in $CD4^+$ T cell count that resulted in a decrease in inflammation and an improvement in clinical symptoms. Besides this immediate effect, the infusion of stem cells after high doses of immunosuppression gave rise to a new tolerance system. Another proposition showed that the ability of a patient to improve was because the stem cells were able to differentiate into glial cells and some neuronal precursors, thus contributing to the repair of injured neural tissue. Therefore, stem cell transplant can decrease the severity of disease progression in multiple sclerosis. (Rosa SB, 2007)

The European Society for Bone Marrow Transplantation, European League against Rheumatism, and the Autologous Stem Cell Transplantation International on Multiple Sclerosis Trial were aimed at comparing stem cell transplant with regular treatment to determine its potency and the harmfulness associated with the transplant therapy in patients with progressive multiple sclerosis. Another controlled clinical trial (MIST), initiated by R. Burt in Chicago in collaboration with some Brazilian centers, compared Autologous Hematopoietic Stem Cell Transplant with regular treatment in the earlier inflammatory phase of interferon-refractory diseases (relapsing-remitting subtype). (Hough RE;2005)

In the Brazilian cooperative trial of Autologous Hematopoietic Stem Cell Transplant for Autoimmune Diseases, about forty-one patients with primary progressive or secondary progressive MS with a score of 7.0 on Expanded Disability Status Scale had a stem cell transplant from June 2001 to August 2006 at several medical school hospitals. At first, twenty-one patients were given chemotherapy(1,3-bis[2-chloroethyl]-1-nitrosourea, etoposide, aracytin, melphalan), and horse Anti-thymocyte globulin, and 14.3% died from the complication associated with the transplant. As at 2004, a change was made to the chemotherapy regime to cyclophosphamide (CY) plus Anti-thymocyte globulin, there were no deaths recorded among twenty patients transplanted and there was no difference in the rate of progression of the disease between the two groups before and after the change in the regime. About Eight patients transplanted out of strong immunosuppression either died or showed rapid neurological progression. (Rosa SB;2007)

Systemic Sclerosis (Scleroderma)

Scleroderma is a rare autoimmune multisystemic disorder mostly of unknown etiology affecting the skin, lungs, intestines, musculoskeletal, heart, and the kidneys. It is more common in females than in males, usually presenting from young adulthood (20 - 40 years of age). Although the etiology is unknown, there are evidences supporting genetic involvement, infections such as Human Herpesvirus-4, Parvovirus-B19, Organic solvents, and some chemotherapeutic drugs (Bleomycin and Taxanes). (Ferri C, 1999; Sharma et al., 2004; Farrant et al., 2004; Kettaneh et al., 2007)

There are two known types of scleroderma; Limited and Diffuse. The Diffuse type is the most common accounting for 80% of cases and the Limited type accounts for 20% of cases. The Limited type is also known as C.R.E.S.T: *Calcinosis, Raynaud, Esophageal dysmotility, Sclerodactyly, Telangiectasia.*

The overproduction and deposition of collagen by fibroblasts in various tissues and organs is responsible for this condition regardless of the suspected risk factors. This process is initiated by activation of T-cells that subsequently secrete cytokines and chemokines such as TGFs: Transforming Growth Factors(TGFs) and common tissue growth factors whose over-production and over-expression appear to activate intracellular secondary messengers such as SMAD-2, SMAD-3 and SMAD-4 that play an important role in collagen production in organs (Warren et al., the textbook). In systemic sclerosis, there is a concept of microchimerism where fetal cells in maternal circulation are believed to be responsible for collagen deposition.

Antibodies produced in Systemic sclerosis are Anti-Scl-70 antibodies. In the Diffuse subtype, anti-topoisomerase antibodies are usually seen whereas, in the Limited subtype, anti-centromere antibodies are seen. Anti-nuclear antibodies can be seen in both subtypes, and these antibodies play an integral role in the diagnosis of the disease. These anti-nuclear antibodies are further buttressed by their roles in the endothelial injury at the outset of the disease and show documented evidence in the activation of platelet aggregation and Type 2 hypersensitivity reactions (Jimenez et al., 2004; Fonseca et al., 2007; Warren et al.; 2020).

A high level of morbidity and mortality is caused by extreme forms of the disease because there is no cure, 40 - 50% of which are due to the involvement of the kidneys, lungs and heart. The fibrosis seen in the disease cannot be reversed by Conventional therapies. Conventional therapies are not curative but are used in improving patient's quality of life, and reduce the progression of disease in some cases.

Clinical presentation of Scleroderma

System	Presentation
Raynaud Syndrome	Vascular reactivity of the finger preceded by pain, cyanosis, or pallor. Worse with cold weather and Stress (Emotional). It can be complicated by Ulceration and Gangrene. Treated with calcium channel blockers like nifedipine, prostacyclin analogue (iloprost, bilprost), endothelin receptor blocker (bosentan).
Skin Involvement	Face, hand, neck, and leg fibrosis. Blood vessel dilation (telangiectasia) and hyperpigmentation. Treated with Cyclosporin and methotrexate
Gastrointestinal	Gastroesophageal reflux disease caused by Esophageal dysmotility, small and large bowel diverticulum. Treated with proton pump inhibitors
Renal	Sudden rise in Blood Pressure (Malignant hypertensive emergency/crises) with features of acute renal failure azotemia, uremia, hyperkalemia. Treated with angiotensin-converting enzyme inhibitors like captopril, lisinopril and dialysis.
Lung	Lung fibrosis leading to loss of lung compliance. Restrictive lung disease and Cor-pulmonale. Pulmonary hypertension usually associated with BMPR-2 gene mutation and CREST Syndrome. Treated by cyclophosphamide, calcium channel blockers like nifedipine, prostacyclin analogue (iloprost, bilprost), endothelin receptor blocker (bosentan) and Nintedanib
Cardiac	Pericarditis, Fibrosis of the myocardium, Right ventricular hypertrophy, and Heart block.

Cases of 83 patients diagnosed with Systemic sclerosis were submitted for stem cell transplantation were registered in Europe and the United States. The treatment method done with Autologous hemopoietic stem cells (AHSCT) registered in EULAR/EBMT was similar, hence this therapeutic regime is used. The use of Cyclophosphamide and G-CSF is preferred to that of G-CSF in cell mobilization. 87% of patients had a selection of $CD34^{+}$ before reinfusion was performed. 90% of cases had Cyclophosphamide either as monotherapy or

Cyclophosphamide plus ATG, 36 patients had the combination and by 1996, satisfactory results have been obtained in patients after transplantation using hemopoietic stem cells (Van Laar JM, 2004; Farge D, 2004; Tsukamoto H, 2006).

In another study conducted by Farge et al., 57 patients diagnosed with Systemic sclerosis were treated with stem cell transplantation and follow up for 6 years (1996 - 2002). 14 of these patients had complete remission and 32 had partial remission. Despite the treatment with HST, some patients still exhibited active disease and are in worse condition than they were before the start of HST. In a French study conducted in Multicentre involving 11 patients, 8 had a partial or complete response and 5 had a reactivation of the disease. Based on the findings of these studies, it can be deduced that not all outcomes are favorable in the treatment of Systemic sclerosis with stem cells. The authors however agreed that stem cell therapy can extend the life expectancy of patients with severe cases. The risk of toxicity was not analyzed due to the small sample size. Immunosuppressors at high doses were less tolerated by patients with pre-existing lung or heart conditions due to the cardiotoxic effects of Cyclophosphamide. The use of thiotepal and a low dose of Cyclophosphamide is said to minimize the Cyclophosphamide (CY) induced cardiotoxicity. To reduce the number of deaths, the patient should be carefully selected, monitored during treatment and appropriate changes should be made in the transplantation protocol. (Rosa SB,2007)

Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, a controlled randomized study in Phase III which is being conducted under the supervision of EBMT and EULAR. The objective of this study is to investigate the effect of administering intensive immunosuppression followed with hematopoietic stem cell therapy (HSCT), compared to the conventional therapy of chemotherapy and Cyclophosphamide in scleroderma patients, in the name of safety and being an effective protocol (Hough RE et al., 2005).

In the Brazilian Cooperative trial of AHSCT for autoimmune diseases; amongst 7 patients with systemic sclerosis (both refractory and progressive), 2 improved and 1 out of the 3 that were mobilized but not transplanted died from infection. Another patient who had pre-existing SLE, now presenting with systemic sclerosis died from reactivation of pulmonary and cerebral vasculitis. 3 improved

significantly after transplantation, their pulmonary function tests became stabilized and the skin became soft (Rosa SB, 2007). In a future follow up, it was reviewed that 1 patient from the 3 that improved after transplantation died of pulmonary infection 2 years after. The other 2 patients that had undergone transplantation at the São Paulo Hospital in Ribeirão Preto had no complications and improvement of their skin lesion was rapid. The Brazilian clinical trial further reinstates that stem cell treatment is far from 100% curative and does not show an excellent response in the treatment in systemic sclerosis. (Rosa SB, 2007)

Autoimmune Cytopenia

Autoimmune thrombocytopenic purpura (AITP) is a disease caused by platelet sensitization by antiplatelet antibody or by circulating immune complexes, thereby provoking the early removal of the affected cells from the body. The process of removal results in thrombocytopenia and bleeding (Rosa SB, 2007).

It is important to differentiate HUS (Hemolytic Uremic Syndrome) alongside Autoimmune thrombocytopenic purpura (AITP) or Thrombotic thrombocytopenic purpura (TTP) because they have similar presentations and show only little differentiating factors.

	HUS	TTP/AITP
Pathology	Non-autoimmune (infection)	Metalloproteinase ADAMTS 13 gene mutation.
Etiology/association	E. coli 0157:H7, frequent in children.	Ticlopidine, clopidogrel, cyclosporine, AIDS, SLE. Commoner in adult neurological symptoms such as seizure and confusion.
Thrombocytopenia	Yes	Yes
PT/aPTT	Normal	Normal
Negative coombs test	Yes	Yes
Renal insufficiency	Yes	Yes
Schistocyte (fragmented RBCs from hemolysis)	Yes	Yes

Treatment	Plasmapheresis/Plasma exchange for severe cases. Steroids for cases unrelated to diarrhea. Eculizumab for cases unrelated to infection.	Steroids for cases unrelated to drugs.
Contraindications	Replace with fresh frozen plasma (FFP) if plasmapheresis is delayed. Never should Platelet be transfused in HUS or TTP patient. It will worsen the patient's condition.	Same

In a study conducted which describes the clinical history of patients registered in the EBMT, these patients received hematopoietic stem cell therapy (HSCT) as a treatment for severe refractory autoimmune cytopenia. 12 patients with Autoimmune thrombocytopenic purpura (AITP) were submitted for transplantation (autologous) and their responses to transplantation were tremendously diverse. It varied from transient continuous remission to death, all of which were related to transplantation (Urban C, 2006). 14 patients with chronic refractory AITP in the United State (US) were allocated to high dose cyclophosphamide (200mg/kg), after which they received AHSCT. Six had complete responses and two achieved a partial response (Hunh RD, 2003). A conclusion was drawn that the infusion of hematopoietic stem cells (HSCs) put on a spurt on the hematological restitution. However, since the improvement was not associated with the amount of anti – GPIb/anti-GPIIIa antibodies, this shows that there are no other antiplatelet/platelet antigens involved in AITP/TTP. Also, there was no known correlation between the number of associations and responses, but the deletion of T lymphocyte might have prevented the auto-reaction of T cell to the re-infusion (Rosa SB, 2007).

A clinical trial with a larger sample size of patients could prove and provide more reliable information. It would help researchers understand the importance of lymphocyte deletion characterization in a patient's genetic profile, helping identify those responsive to and those not responsive to treatment. This comparison enables practitioners to diverge through various treatment protocols, such as; (I) Therapy based on only high dosage of CY, (II) High dose of CY in combination with stem cell transplantation or (III) High dose of CY in combination with stem cell transplantation and agent that induces maintenance of post-transplantation tolerance (Lim SH, 1997).

Autoimmune Hemolytic Anemia (AIHA)

It is important to understand that all form of hemolysis will lead to the following changes;

1. A decrease in the number of Hematocrit (Hct).
2. Increase lactate dehydrogenase, indirect bilirubin, reticulocyte count, and decrease serum haptoglobin level.
3. A slight decrease in Mean corpuscular volume (MCV) due to the increased Reticulocyte count.
4. Hyperkalemia form cell lysis.
5. Folate deficiency from an increase in cell production. (folate storage is limited).

Disease	Hemolytic Anemia
Etiology	50% are idiopathic. Chronic lymphocytic leukemia/Lymphoma, SLE, Drugs: (alfa-methyldopa, Penicillin, Phenytoin, Rifampin).
Diagnostic Test; Most Accurate	Coombs test (detects IgG antibody on the surface of RBC)
Associations	Microspherocytosis
Treatment Options	
Best Initial Therapy	Glucocorticoid; Prednisolone
Recurrent episodes	Splenectomy
Severe, acute hemolysis refractory to Prednisolone	Administer intravenous Immunoglobulin (IVIGs) to the patient
Recurrent Hemolysis refractory to Splenectomy	Administer Rituximab, azathioprine, cyclophosphamide/cyclosporine to such patient.

AIHA is caused by the early destruction of erythrocytes (RBC), caused by the fixation of Immunoglobulins/Complement proteins on the surface of the RBC membrane. The initial presentation includes; anemia induced hemolysis secondary to hemolytic condition or the diseases causing AIHA as mentioned in the table above.

A few scientific literature reports in which stem cell transplantation has been used to successfully treat AIHA patients suggested that post-transplantation immunosuppressive therapies should be used. In defiance of the emergent data, stem cell transplantation offers a new possibility for AIHA patient treatment or therapy (Hunh RD, 2003; Seeliger S, 2001).

Dermatomyositis

Dermatomyositis is a rare immunologically mediated disease of unknown etiology in which damage to small blood vessels contribute to injury and inflammation of muscle and skin. Dermatomyositis belongs to a heterogeneous group of 3 autoimmune rheumatological diseases termed idiopathic inflammatory nonsuppurative myopathies, which also include polymyopathy and inclusion body myopathy however. The role of inflammation in inclusion body myopathy is unclear (Dalakas MC, 1991; Ramos-E-Silva M, 2016).

Dermatomyositis and Polymyositis show typical clinical features of autoimmune inflammatory disease and associations with auto-antibodies particularly HLA-DR genotype and other autoimmune disorders. Overlapping forms of inflammatory myopathies that defy a precise classification have also been identified. The clinical response to steroids and other immunosuppressive agents helps to distinguish inflammatory myopathies from other causes of myopathies (Callen JP, 2006).

Dermatomyositis occurs in both children and adults. It is however most common in women. It is a multisystemic rheumatologic disease that commonly presents with muscular and cutaneous symptoms, and in 20 – 25% of patients, dermatomyositis is associated with malignancy. (Ramos-E-Silva M,2016) Diagnosis is usually made from the clinical manifestations, elevated blood enzymes, autoantibody

testing, and muscle biopsy. There is no cure for dermatomyositis, but corticosteroids, immunosuppressive agents, and intravenous immunoglobins are routinely used for treatment.

Variants of Dermatomyositis:

- Classical Dermatomyositis: muscle and joint involvement with characteristic skin involvement, like violaceous erythematous rash called malar rash, purple/erythematous called heliotrope rash, raised papules in the joint called Gottron papules, periungual /cuticular vascular dilatation and shawl sign(poikiloderma) which is atrophy, reddening, and dyspigmentation in the face, neck and upper chest.
- Amyopathic Dermatomyositis with no muscle involvement.
- Hypomyopathic dermatomyositis, the patient has no evidence of muscle symptoms more than 6months.
- Juvenile dermatomyositis usually occurs before 16 to 18 years.
- Polymyositis is strictly muscular and joint involvement without skin manifestations.
- Adermatopathic subtype, where there is no histological evidence despite classical clinical manifestations.

Demographics: Incidence of 2 - 10/million per annum.

Juvenile and adult forms are recognized. Hence the disease has a bimodal age of onset before 16 years of age and after 40 years of age. The juvenile age of onset is 7 years in the USA, with 3 new cases per year (3000 to 5000 children). Dermatomyositis is the most common inflammatory myopathy in children.

The adult form of the disease commonly occurs between the 4^{th} and 6^{th} decade of life, with 10 new cases per year among adults. There is a higher incidence in females >2:1 with a peak age of 40 to 50 years of age. Black to White ratio of 4:1 is noted, but the incidence is higher among Japanese.

Dermatomyositis is an autoimmune, non-contagious, inheritable disease associated with MHC class 2 genes acting via HLA-B8/DR3, DR6 and DR52 as a result of producing antibodies like anti-nuclear antibody (ANA, 80%), Rheumatic factors (Rh factor, 10%), Anti-Mi (skin manifestations) others but most specifically Antisynthetase antibody called Anti-Jo1(20 -50%) (Ramos-E-Silva M, 2016).

The following criteria are enough to make a diagnosis of Dermatomyositis as proposed by Bohan and Pete (1975)

- Progressive proximal symmetrical weakness
- Elevated levels of muscle enzymes
- An abnormal finding on electromyography
- Abnormal muscle biopsy findings
- Skin manifestations: The presence of the skin involvement differentiates Dermatomyositis from another idiopathic inflammatory myositis like Polymyositis, Inclusion body myositis, and other myopathies (Gerami P, 2006).

Clinical manifestations :

Patients with dermatomyositis commonly present with proximal muscle weakness that is slow in onset and associated with myalgias, with the shoulder and hip joints mostly affected. Getting up from chairs and climbing stairs become increasingly difficult in patients. Fine movements controlled by distal muscle may be affected only late in the disease. Others are;

- Cutaneous symptoms: heliotrope rash – a lilac(purple)0 colored discoloration of the eyelids with periorbital edema (90%), malar rash, Gottron papules – roughened red papules, scaling erythematous eruption or dusky red patches over knuckles, elbows, and knees, photosensitivity.
- Oropharyngeal muscle weakness which manifests as dysphagia, dysphonia and a nasal voice and esophageal dysmotility (10-30%)

- Raynaud's phenomenon
- Arthralgia/arthritis (20%)
- Interstitial lung disease (>20%)
- Myocardial involvement (myocarditis, arrhythmias and abnormal EKG)
- Constitutional symptoms such as fever and weight loss
- Associated malignancy including breast, colon, lung, ovarian, melanoma, non-Hodgkin, nasopharyngeal (Asians), and gastric (Westerns) can occur 5 years after the onset of symptoms. Occasionally, malignancy may predate myositis. Screening for malignancies is thus mandatory in patients.

Most developing countries are not well equipped to make a definitive diagnosis, which accounts for a lack of data about the disease. It is thus imperative for physicians to have a high index of suspicion because of the excellent clinical response to the administration of corticosteroids in most cases with early detection (Pachman et al., 2019).

A variety of enzymes are elevated in dermatomyositis. Creatine Kinase (CK), Lactate dehydrogenase (LDH), Aspartate transaminase (AST), Alanine transaminase (ALT), and Aldose are commonly elevated due to muscle damage, but CK and Aldolase are the most sensitive. Complete blood count (CBC) may show lymphocytosis, especially during flare-ups, while Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated. Myoglobinuria is rarely seen (Ramos-E-Silva M, 2016).

Autoantibody Association findings: (Quain RD, 2006; Tersiguel AC, 2014)

- ANAs positivity is seen in >80% of patients,
- Rheumatoid factor is usually positive in 50% of patients.

- Anti-Mi-2 antibodies- seen in <5% of patients, they show a strong association with prominent Gottron papules and heliotrope rash.
- Anti-tRNA synthetase antibody (Anti Jo-1,) – directed against the enzyme histidyl t-RNA synthetase, is more specific and seen in more than 80% of the patients especially in those likely to develop interstitial lung disease, non-erosive arthritis, and mechanic's hands.
- Other rarely found antibodies in dermatomyositis are anti-TIF1y, anti-NXP2, anti-SAE all associated with pulmonary fibrosis, anti-P155/P140 antibodies directed against transcription factors, and anti-MDA5 (rarest).

Electromyography may show abnormality in active myositis and normal finding in the inactive stage of the condition. A triad of changes are usually seen in active myositis;

- Spontaneous fibrillation potentials at rest
- Short-duration potentials on voluntary muscle contraction
- Repetitive potentials on mechanical stimulation of the nerve.

Muscle biopsy confirms the diagnosis and will show predominant mononuclear inflammatory cells (B-cells and CD4+cells lymphocytic infiltrates) in perifascicular/perimysial region and around blood vessels, unlike in polymyositis which shows CD8+ cells more in the endomysial region. Perifascicular myofiber atrophy and segmental fiber necrosis and regeneration are also seen (Bohan A, 1977).

Immunohistochemical studies may reveal T lymphocyte cell-rich infiltrate and deposition of complement membrane attack complex (C5b-9) in capillary beds in affected tissue. Electron microscopy shows tubuloreticular endothelial cell inclusions. Other investigations mostly useful in the evaluation, of course, complications and associated malignancies include Papanicolaou smear, urinalysis, CA-125,

fecal occult blood testing (FOBT), chest X-ray, CT-Scan of the abdomen and pelvis, and PET Scan. (Philip N, 2008; Ramos-E-Silva M, 2016)

Clinical management of dermatomyositis is mostly suppressive with anti-inflammatory and immunosuppressive agents. Pharmacological and non-pharmacological therapy are available to reduce morbidity and mortality and improve the quality of life in patients. There are also ongoing clinical trials to find a possible cure for dermatomyositis, with stem cell transplant and cannabinoid receptor type 2 (CB2) agonist medications (Drake LA,1996).

Non-pharmacological therapy usually involves psychiatric evaluation and counseling, bed rest, physical therapy in the form of graded exercise programs, plasmapheresis, and occupational therapy. (Alexanderson H, 2005; Ramos-E-Silva M, 2016) Pharmacological treatment currently includes the use of corticosteroids (oral prednisone) as first-line therapy. Immunosuppressive agents (azathioprine, methotrexate) are used as second-line therapy for steroid-resistant cases or as steroid-sparing agents. Third-line treatment options include intravenous immunoglobulin, cyclophosphamide, cyclosporin, mycophenolate mofetil, biological agents (infliximab, rituximab, and etanercept). Supportive treatment options in patients include topical tacrolimus and hydroxychloroquine for skin disease, vitamin D supplementation and use of bisphosphonates, and chemoprophylaxis for pneumocystis pneumonia (Dourmishev et al.,1999; Sultan SM, 2002; Ramos-E-Silva M, 2016).

The mortality rate was pretty high, up to 50% mortality before the advent of the use of corticosteroid therapy. The mortality rate is also higher in the presence of co-morbidities like old age > 65 years, cancer, lung, and cardiovascular diseases. The 5-year survival for adult patients without major complications is however good at about 90%. Overall prognosis is better in children than in adults (Coyle KM, 2008; Oddis CV, 2002; Sultan SM, 2002)

Autologous bone marrow transplantation, with depleted CD3/CD19, successfully treated 2 patients after immoablation with fludarabine, cyclophosphamide, and anti-thymocyte globulin. Patients with refractory respond to immune ablation with Campath-1H (anti-CD 52) antibody alone in a bid to reduce cost and damage to BMT (Pachman, L.M., 2018).

Amyotrophic lateral sclerosis (ALS)

This is an extremely fatal neurodegenerative disease characterized by loss of motor neurons in the cortex, brain stem, and spinal cord. The etiopathogenesis is not well understood but there are postulation favoring several altered signaling pathways like glutamate excitotoxicity, mitochondrial dysfunction, oxidative stress, and neuroinflammation (Bonafede R., 2017). It is a progressive disease in an adult with both upper and lower motor neurons paralysis. The life expectancy is 3 - 5 years, with a majority of cases which are sporadic in nature, while as few as 5 - 10% presenting with family history. The median age is reported to be around 65 years with the onset of 10 years earlier. As the disease progresses there is degeneration of the corticospinal tract and loss of innervation to muscles. The most common cause of death in ALS is respiratory failure. Cognitive and behavioral changes are seen in about 50% of cases, while frontotemporal dementia may be seen about 5-10% of cases (Renton AE, 2014; Van Es MA, 2017). The mechanism is not well understood, but there is evidence supporting mutation in more than 30 genes in the familial subtype. The defective genes are shown to affect the control signal in axonal transport, protein turnover, and RNA activities (Robberecht W, 2013).

The most common genetic abnormalities in ALS are *C9ORF72* (40%), *SOD1* (20%), *FUS* (1–5%), and *TARBDP* (1–5%). A recent study (Burk K, 2019) showed more evidence that these genes played important roles in the development of ALS by;

- Disrupting receptor and endosomal trafficking with transport system disruption
- Hexanucleotide repeat expansion and expression of TDP-43 and Alsin-2
- Autophagy dysregulation with aggregates formation linked to mutation of ubiquitin-2
- Transport system disruption from the endoplasmic reticulum and the Golgi apparatus

- Impaired nucleocytoplasmic transport with the accumulation of TDP-43
- Mislocalization of NPC (associated with SOD1 mutation) clogging of DPRs

Diagnosis is difficult to make and the following investigations like electromyogram, nerve conduction test, brain MRI, blood workup, lumbar puncture, and muscle biopsy are carried out. Currently, there is no definitive cure for ALS, but it is primarily managed by physical therapy, breathing care, speech-occupational-psychological, and physical therapy. Medications employed in the treatment of the disease are glutamate antagonist (Riluzole) and neuroprotective agent (Edaravone) are not curative.

These therapies are incapable of restoring neuronal loss. Recent studies are showing lots of promises in replacement of lost neurons as against the belief that neurons are out of the cell cycle and are not regenerative. Umbilical stem cells are now alternative to adult neural stem cells which are difficult to extract. The cells can be expanded ex-vivo and use in the treatment of ALS. (Silani V, 2004).

In vitro transdifferentiation of human HSCs from UCB to neurons has been demonstrated, and astrocytes are formed in a suitable microenvironment. Cogle et al. showed differentiation of neural cells to neurons, astrocytes, and microglial. Although there are limitations and controversy in the use of stem cells to cure ALS, a study on mice with spinal cord injury shows a reversal of the paralysis by injecting human ESCs into the cepalorachidian liquid of SOD1 mice. (Vastag. B et al., 2001)

Most clinical studies in the trials of stem cell treatment of ALS have shown to have adequate delivery of trophic and growth factors, a conducive environment for cellular expansion and serving as protective agents against neurotoxic substances (Silani V, 2004). The majority of the trials employed the use of autologous stem cell injection directly into the brain and spinal cord. Some of the trials done demonstrate the use of what Jason et al. used HSCs (CD 34+) on 3 patients and they observed partial to mild effect on the CNS and absence of complications.

In another study at the University of Turin, where autologous MSCs from bone marrow were used on 7 patients. The results showed improvement in muscle function in 4 patients, minimal improvement in 2, improvement in breathing in 4 patients, all after 2 years (Mazzini L, 2004).

A report of embryonic stem cells obtained 4 to 6 weeks use in 61 patients with ALS, shows a 34 % improvement within 2 months. HSCs collected from peripheral blood was used by a researcher in Montevideo, Uruguay with 12 ALS patients showed encouraging improvement in 3 and stability achieved in 9. (De Bellis R, 2006)

A report was sent to the European Registry of HSCT for AD (EBMT/EULAR, based in Basle, Switzerland) of 2 patients submitted to AHSCT in France (Tyndall A, personal communication) who underwent treatment with the use of HSCT and high dose immunosuppressants were discouraging as they both died after 7 months. If comparisons were to be made of the Baylor College of Medicine USA research trial involving 6 patients, who received allogeneic BMT from their HLA-identical siblings, 3 patients show stability, 2 of them died and 3 patients showed no benefit (Rosa SB, 2007; Appel SH, 2004).

Contrary to the results obtained from the study in France, AHSCT for ALS in Brazil in December 2004 at the University Hospital of the School of Medicine of Ribeirão Preto for 2 patients with the use of immunosuppressants like cyclophosphamide (CY), fludarabine and ATG, one died and the other was alive for 28 months after transplantation. A more elaborate study on 15 patients with the use of AHSCT in a Salvador hospital shows 3 transplant-related deaths, 1 transplant unrelated death and 10 patients alive at a mean follow-up of 133 days (Rosa S.B, 2007).

2.2: Review of Empirical Evidence

Incidence of Autoimmune diseases

The most recent large-scale study to determine *incidence* rates for autoimmune diseases was published in 1997 by Jacobsen & colleagues, 1997. The investigators conducted an extensive review of more than 140 studies published between 1965 and 1995 that provided incidence estimates for autoimmune diseases. Controlled studies were available for only 24 of the estimated 80 autoimmune diseases. Based on data from these studies, Jacobsen *et al*. estimated an annual incidence of 1.3 new cases for every 1,000 females and 0.5 new cases for every 1,000 males in the United States in 1996. Also, it was estimated that 8,511,845 persons in the United States or approximately 1 in 31 Americans are currently afflicted with one of these autoimmune diseases. Although this study has stimulated additional epidemiological research on autoimmune diseases, it has several important limitations. Many of the source studies were conducted more than two decades earlier and other evidence now suggests that the incidence of many autoimmune diseases is increasing. The study focused on small populations in geographically localized areas and contained only limited information on different populations. Further, diagnostic criteria used to identify and confirm cases varied substantially among different studies of the same autoimmune disease, hindering cross-study analyses. The diseases with the highest prevalence rates were Graves'/hyperthyroidism, IDDM, pernicious anemia, rheumatoid arthritis, thyroiditis, and vitiligo, comprising an estimated 7,939, 280 people or 93% of the total number estimated. Glomerulonephritis, MS, and SLE added an estimated 323,232 people. The prevalence of the other diseases reviewed were rare, less than 5.14/100,000. Most diseases were more common in women. From the incidence data, it was estimated that 237,203 Americans will develop autoimmune diseases in 1996 and that approximately 1,186,015 new cases of these autoimmune diseases occur in the United States every 5 years. Women were at 2.7 times greater risk than men to acquire an autoimmune disease.

Aaron *et al*., (2015) conducted a systematic review to calculate the percentage (%) increases per year of autoimmune disease frequencies worldwide, analyze the differential increases per country and disease, and identify geo-epidemiological trends. The study utilized search engines such as Medline, Google, Cochrane Library databases, and 30 Studies from the last 30 years were identified. Findings from the study showed that the means ± S.D. of the net % increased per year incidence and prevalence of autoimmune diseases worldwide were 19.1±43.1 and 12.5±7.9, respectively. Rheumatic, endocrinological, gastrointestinal, and neurological autoimmune diseases revealed the following annual % increases per year: 7.1, 6.3, 6.2, and 3.7, respectively. In all of these, differences between old vs new frequencies

were highly significant ($p < 0.0001$). Comparing various autoimmune diseases, celiac disease increased the most and the highest increase in incidence, comparing old to new surveys are allocated to myasthenia gravis. Despite considerable variations between the countries, celiac, type 1 diabetes, and myasthenia gravis frequencies increased the most in Canada, Israel, and Denmark, respectively. Frequencies of the autoimmune diseases increased significantly in the West and North when compared to East and South, respectively (Lerner, Jeremias, & Matthias, 2015).

Social demographic characteristics of individuals who have autoimmune diseases

Jacobsen *et al*., (1997) also reviewed more than 130 published studies in an effort to estimate the *prevalence* of autoimmune diseases. From this analysis, the investigators estimated that in 1996, 8.5 million people in the United States – 3.2 percent of the population – had at least one of the 24 autoimmune diseases evaluated in their studies. Current estimates of the prevalence of all autoimmune diseases range from 5 to 8 percent of the U.S. population; this corresponds to between 14.7 and 23.5 million people, based on August 2004 Census Bureau figures. More recently, Cooper and Stroehla (2003) extended the Jacobsen analysis by examining incidence and prevalence data on autoimmune diseases that were not included in the 1997 study. In this study, the investigators confirmed the disproportionate occurrence of these diseases among women and noted that the temporal pattern of incidence differs among the autoimmune diseases that have been studied most extensively. For example, the incidence of type 1 diabetes has increased worldwide over the past 40 years, while the incidence of rheumatoid arthritis seemingly has declined during this time period.

Only one study has estimated total mortality from autoimmune disease in the United States. Using data for 1995 from the CDC's National Center for Health Statistics, Walsh & Rau (2000) found that well-defined autoimmune diseases collectively were among the top ten leading causes of death for women in every age group up to 64 years of age and exceeded that for the eighth leading cause in the 15 to 24, 25 to 44, and 45 to 64 years age groups.

Incidence of Type 1 Diabetes (T1D)

Karvonen *et al*., (2000) carried out a study to investigate and monitor attributes in childhood type 1 diabetes incidence globally determined of type 1 diabetes incidence (per 100,000 per year) from 1990 to 1994 in children ≤14 years of age from 100 centres in 50 countries. An overall 19164 cases were diagnosed in study populations of 75.1 million children, whereby the annual incidence rates were calculated per 100,000 populations. The overall age-adjusted type 1 diabetes mellitus(T1D) incidence differed from 0.1/100,000 per year in China and Venezuela to 36.8/100,000 per year in Sardinia and 36.5/100,000 in Finland; thus, representing a >350-fold variation in the incidence among the 100 populations globally. The worldwide pattern of incidence variation was evaluated by arbitrary grouping of the populations with a very low (<1/100,000 per year), a low (1-4.99/100,000 per year), an intermediate (5-9.99/100,000 per year), a high (10-19.99/100,000 per year), and a very high (≥20/100 000 per year) incidence). Among the European populations, 18 of 39 presented an intermediate incidence, and the rest had an elevated or very elevated incidence. An extremely high incidence (≥20/100,000 per year) was detected in Sardinia, Finland, Sweden, Norway, Portugal, the United Kingdom, Canada, and New Zealand (Karvonen *et al*., (2000).

The lowest incidence (<1/100, 000 per year) was realized from China and South America populations. The incidence increased with age and was the highest among children 10-14 years in most populations. The extent of global disparities in childhood type 1 diabetes incidence was greater than previously described. The earlier reported polar-equatorial gradient in the incidence was not ostensibly strong as previously suggested, but the variation apparently took an ethnic and racial distribution in the global population (Karvonen *et al*., (2000).

In examination of the global type 1 diabetes incidence and trends from 1990-1999 the DIAMOND Project Group (2006), analysed type 1 diabetes incidence (per 100,000/year) in children aged ≤14 years from 114 populations in 112 centers in 57 countries. The incidence of type 1 diabetes trends was analysed by fitting Poisson regression models to the dataset. A total of 43,013 cases diagnosed in the study populations of 84 million children, with an age-adjusted incidence of type 1 diabetes among 112 centers (114 populations) varied from

0.1 per 100,000/year in China and Venezuela to 40.9 per 100,000/year in Finland. The average annual increase in incidence calculated from 103 centers was 2.8% (95% CI 2.4-3.2%). During the years 1990-1994, this increase was 2.4% (95% CI 1.3-3.4%) and during the second period of 1995-1999, it was slightly higher at 3.4% (95% CI 2.7-4.3%). The trends estimated for continents depicted statistically significant increases worldwide (4.0% in Asia, 3.2% in Europe, and 5.3% in North America), excepting Central America and the West Indies where the trend decreased by 3.6%. The trend in incidence diminished with age only among the European populations. The increasing global type 1 diabetes incidence suggestively necessitates continuous monitoring of incidence by the application of standardized procedures for planning or assessment of prevention strategies.

The SEARCH for Diabetes in Youth Study recently published a set of papers in a supplement to *Diabetes Care* in which race and ethnic-specific issues in diabetes in 9,174 American youth are reviewed for five major race and ethnic groups in the U.S., non-Hispanic white, African American, Hispanic, Asian and Pacific Islander, and Navajo populations (Mayer *et al*., 2009; Bell *et al*., 2009; Lawrence *et al*., 2009; Dabelea *et al*., 2009). In these papers, the authors estimate the prevalence and incidence of diabetes in youth <20 years by age, sex, race/ethnicity, and diabetes type as well as characterize key risk factors for diabetic complications by race/ethnicity, and diabetes type (Mayer *et al*., 2009; Bell *et al*., 2009; Lawrence *et al*., 2009; Dabelea *et al*., 2009)

In the non-Hispanic white population, the prevalence of Type One Diabetes (T1D) was 2.0/1,000 and the incidence was 23.6/100,000 (with a slightly higher incidence rate for males than females (24.5 v 22.7 per 100,000, respectively, p=0.04). The authors conclude that these rates of T1D among non-Hispanic white youth are among the highest in the world. These youth had adverse cardiometabolic risk profiles (>40% with elevated LDL, <3% met dietary recommendations for saturated fat, and among those ≥15 years of age 18% were current smokers) which put them at risk for future health complications related to diabetes (Mayer *et al*., 2009; Bell *et al*., 2009; Lawrence *et al*., 2009; Dabelea *et al*., 2009)

.

In African American youth in the SEARCH study, the prevalence of type 1 diabetes mellitus(T1D) was 0.57/1,000(95% confidence interval (CI) of 0.47– 0.69) for youth age 0–9 years and 2.04/1,000 (CI of 1.85–2.26) for youth 10–19 years. The incidence of T1D for 0–9-year-old and 10–19-year-old during 2002–05 was 15.7/100,000. Of the African American youth that attended the research visit with T1D, 50% of those ≥15 years had A1c ≥9.5% and 44.7% were either overweight or obese (Mayer *et al*., 2009; Bell *et al*., 2009; Lawrence *et al*., 2009; Dabelea *et al*., 2009)

.

The incidence of T1D in Hispanic youth in the SEARCH study was 15.0/100,000 and 16.2/100,000 for females and males 0–14 years of age. Poor glycemic control as well as high LDL-cholesterol and triglycerides were common and 44% of these youth with T1D were overweight or obese.

The incidence of T1D among Asian and Pacific Islander youth was 6.4 and 7.4/100,000 person-years in 0–9 and 10–19 years old, respectively. The Pacific Islanders were more likely to be obese as compared to the Asian or Asian-Pacific Islanders (mean BMI 26 v 20 kg/m2, $p<0.0001$).

The majority of Navajo youths that were identified as having diabetes were diagnosed with type 2 diabetes mellitus(T2D) (66/83 in the SEARCH paper). The authors state that T1D is present in Navajos, but that it is infrequent and estimates that the prevalence of T1D in Navajo youth is <0.5/1,000 and the incidence <5/100,000 per year. Regardless of type, Navajo youth were likely to have poor glycemic control and a high prevalence of unhealthy lifestyle and depressed mood (Mayer *et al*., 2009; Bell *et al*., 2009; Lawrence *et al*., 2009; Dabelea *et al*., 2009).

Christopher *et al*., (2019) carried out a review with an objective to describe the methods, results, and limitations of the International Diabetes Federation (IDF) Diabetes developed for the 8th edition estimates of prevalent cases and to provide more detail and analysis of the incidence and prevalence estimates for the 9th edition. The study involved published literature is in the form of incidence rates derived from registers of newly-diagnosed cases. After a systematic review of the published literature and recent conference abstracts, identified studies were quality graded. If no study was available, extrapolation was used to assign a country the rate from an adjacent

country with similar characteristics. Estimates of incident cases were obtained by applying incidence rates to United Nations 2019 population estimates. Estimates of prevalent cases were derived from incidence rates after making allowance for higher mortality rates in less-developed countries. The study reported that the Incidence rates were available for 45% of countries (ranging from 6% in the sub- Saharan Africa region to 77% in the European region). Worldwide annual incidence estimates were 98,200 (128,900) new cases in the under 15-year (under 20 years) age-groups. Corresponding prevalence estimates were 600,900 (1,110,100) existing cases. Compared with estimates in earlier Atlas editions, numbers have increased in most international diabetic federation (IDF) regions, reflecting incidence rate increases, but prevalence estimates have decreased in sub-Saharan Africa because allowance has been made for increased mortality in those with diabetes.

Socio-demographic characteristics of individuals who have Type 1 Diabetes (T1D)

Although most common autoimmune diseases disproportionately affect females, on average girls and boys are equally affected with T1D in young populations. A distinctive pattern has been observed such that regions with a high incidence of T1D (populations of European origin) have a male excess, whereas regions with a low incidence (populations of non- European origin) report a female excess. Many reports indicate an excess of T1D cases in male adults after the pubertal years (male-female ratio ≥1.5) in populations of European origin (Soltesz *et al*., 2007; Green *et al*., 1992; Karvonen *et al*., 1997; Gale *et al*., 2001).

T1D is the major type of diabetes in youth, accounting for ≥85% of all diabetes cases in youth < 20 years of age worldwide (Vandewalle *et al*., 1997; Thunander *et al*., 2008). In general, the incidence rate increases from birth and peaks between the ages of 10–14 years during puberty (EURODIAB ACE Study Group, 2000). The increasing incidence of T1D throughout the world is especially marked in young children. Registries in Europe suggest that recent incident rates of T1D were highest in the youngest age-group (0– 4 years) EURODIAB ACE Study Group 2000). Incidence rates decline after puberty and appear to stabilize in young adulthood (15–29 years).

The incidence of T1D in adults is lower than in children, although approximately one-fourth of persons with T1D are diagnosed as adults. Clinical presentation occurs at all ages and as late as the 9th decade of life. Up to 10% of adults initially thought to have type 2 diabetes are found to have antibodies associated with T1D and beta-cell destruction in adults appears to occur at a much slower rate than

in young T1D cases, often delaying the need for insulin therapy after diagnosis. Individuals diagnosed with autoimmune diabetes when they are adults have been referred to as having latent autoimmune diabetes of adults (Turner *et al*., 1997; Leslie *et al*., 2006; Naik *et al*., 2003).

In 1988, an epidemiological study of type 1 diabetes in Europe the EURODIAB collective group established prospective geographically-defined registers of new cases diagnosed below 15 years of age. The report utilized 16362 cases registered from 1989-94 by 44 centers being representative of most European countries and Israel and encompassing a population of circa 28 million children. The results established an expansive range of incidence rates within Europe and indicated that the rise in incidence during the period differed from country to country. Thus, the accelerated increase of type 1 diabetes in children aged under 5 years remains of particular concern. An identical study Green & Patterson (2001) based on 24423 children, registered by 36 centers, with full participation from 1989-1998 and representing most European countries with population coverage of circa 20 million children, also confirmed the extensively broad range of incidence rates within Europe. Generally, the incidence rate is increasing but is more pronounced in certain regions than in others. There is ostensible seasonality at disease onset even detectable in the youngest age-group.

Case-mortality and morbidity from (T1D)

Norwegian cohort of 1,906 T1D patients diagnosed at <15 years of age between 1973–1982 (46,147 person-years) reported an SMR for all-cause mortality of 4.0 with an SMR of 20 for ischemic heart disease. Acute metabolic complications of T1D were the most common cause of death <30 years of age (Skrivarhaug *et al*., 2006). Similarly, data from the UK report a hazard ratio of 3.7 for annual mortality rates for people with T1D compared to nondiabetics (8.0 v. 2.4/100,000 person-years) with CVD as the predominant cause of death (Soedamah *et al*., 2006). EURODIAB has reported an SMR of 2.0 in 12 European countries that followed 28,887 children with T1D (141 deaths during 219,061 person-years) with a range of SMR from 0– 4.7 among the countries included in the study (Patterson *et al*., 2007).

Incidence of Myopathies/Myositis

A systematic review conducted by Alain *et al*., (2014) aimed at determining the incidence and prevalence of inflammatory myopathies (IMs), their epidemiological tendencies over time, and their possible key determinants. The study utilized All original articles in English or French regarding the prevalence and/or incidence of IMs were searched. The methods of case ascertainment, epidemiological analysis, and diagnostic criteria were systematically analysed. Forty-six articles published between 1966 and 2013 were found in which the incidence of IMs as a whole ranged from 1.16 to 19/million/year and their prevalence ranged from 2.4 to 33.8 per 100 000 inhabitants. Overall IM incidence was estimated at 7.98 cases/million/year (95% CI 7.38, 8.66) between 1951 and 2010 from the results of 16 surveys in which incidence ranged from 1.16 to 19/million/year (95% CI 17, 21). Overall IM prevalence was estimated at 14.00 cases/100 000 inhabitants (95% CI 12.84, 15.46) between 1982 and 2010 from the results of 10 surveys in which prevalence ranged from 2.4 to 33.8/100 000. The relative incidence of DM may follow a latitudinal gradient in the northern hemisphere that may be explained by the immunomodulatory action of ultraviolet radiation. The prevalence of sporadic inclusion body myositis (sIBM) was correlated with the frequency of HLA-DR3. Juvenile myositis onset was non-random over seasons and/or time, consistent with a role of infectious diseases, although other environmental factors may be involved. Disparities according to sex, age, and geographical origin were also found. The frequency of IM increased over time, which may reflect progress in diagnostic performance, although there is still a need to increase the level of awareness with regard to these diseases, especially sIBM, as attested by its considerably delayed diagnosis.

Jun Ann *et al*., (2011) carried out a study aimed at describing the epidemiology of biopsy-proven idiopathic inflammatory myopathies (IIM) in South Australia (SA). Cases of IIM were ascertained by review of all muscle biopsy reports from the Neuropathology Laboratory, Hanson Institute (wherein all adult muscle biopsies in SA are reported) from 1980 to 2009. Clinical correlation of these patients by review of medical records was undertaken. SA population denominator numbers were obtained from the Australian Bureau of Statistics. Findings from the result showed that out of the Three hundred and fifty-two biopsy-proven cases of IIM were identified between 1980 and 2009. The overall annual incidence of IIM appeared to be rising with a mean incidence of eight cases per million

population (95% CI: 7.2–8.9). This corresponded with an increasing annual incidence of inclusion body myositis (IBM) (prevalence of 50.5 cases per million population in 2009, 95% CI: 40.2–62.7).

Socio-demographic characteristics of individuals diagnosed with unspecified Myopathies/Myositis

Jun Ann *et al*., (2011) carried out a study aimed at describing the epidemiology of biopsy-proven idiopathic inflammatory myopathies (IIM) in South Australia (SA). Cases of IIM were ascertained by review of all muscle biopsy reports from the Neuropathology Laboratory, Hanson Institute (wherein all adult muscle biopsies in SA are reported) from 1980 to 2009. Clinical correlation of these patients by review of medical records was undertaken. SA population denominator numbers were obtained from the Australian Bureau of Statistics. Findings from the result showed that

the population group comprised 209 females (59%) and 144 males (41%). Both DM and PM groups demonstrated a female preponderance with an F:M ratio of 2.75 (33 females, 12 males) and 1.55 (110 females, 71 males), respectively. Gender distribution among the IBM group was almost equal with 66 females and 60 males. Also, Inclusion body myositis (IBM) occurred almost exclusively in patients above the age of 50 years (97% of all IBM patients) reaching a peak in the 71–80-year age group.

The youngest IBM patient was 35 years of age. No differential in age groups was observed for Dermatomyositis (DM) or Polymyositis (PM); however, the peak incidence of PM was in the 51–60- year age group. The mean age of DM patients was 55.1 _ 15.8 years (range, 18–90 years) and PM patients 59.0 _13.9 years (range, 18–86 years). IBM patients were the oldest with a mean age of 67.5 _ 10.2 years (range, 35–92 years). The overall incidence rate was highest during the eighth decade and this is likely explained by the high incidence of IBM in this age group. A higher proportion of DM patients reported living in urban dwellings and DM patients tended to be predominantly professionals.

Soo Kyung Cho *et al*., (2019) conducted a study aimed at estimating the incidence and prevalence of idiopathic inflammatory myopathies (IIM) and associated comorbidities in Korea from 2006 to 2015. The study utilized IIM between 2004 to 2015 was identified using the Korean National Health Insurance Service medical claim database. The case definition required more than one visit based on diagnostic

codes including juvenile dermatomyositis (JDM), dermatomyositis (DM), or polymyositis (PM) and registration in the Individual Co-payment Beneficiaries Program (ICBP) for rare and intractable diseases. IIM patients with a disease-free period of 24 months before the index date were defined as incident cases. The Exhauster comorbidity score was calculated. The study findings showed that 1,150 prevalent patients with IIM (117 JDM, 521 DM, 512 PM) were recorded in 2006, and 2,210 (130 JDM, 1,101 DM, 869 PM) in 2015. The prevalence was estimated at 2.3–4.0 (0.9–1.2 for JDM, 1.2–2.7 for DM, 1.4–2.1 for PM)/100,000 person-year (PY). We identified 218 incident cases of IIM in 2006 (18 JDM, 98 DM, 102 PM) and 191 cases (7 JDM, 83 DM, 101 PM) in 2015. The incidence was estimated at 2.9–5.2 (0.7–1.9 for JDM, 1.8–4.0 for DM, 1.6–3.0 for PM)/1,000,000 PY. The mean age (± standard deviation) of prevalent patients with IIM was 51.2 (± 16.9) years, and the percentage of women was 72.1%. More than two-thirds of patients (70.7%) had more than two comorbidities. Twenty percent of patients had interstitial lung diseases.

Incidence of Systemic Lupus Erythematous (SLE)

Eun Hui *et al*., (2020) carried out a study aimed at evaluating the trend of incidence and prevalence of systemic lupus erythematosus (SLE) in South Korea from 2005 to 2015. The study identified cases of SLE from the National Health Insurance Database, which records information on almost all Koreans. SLE was defined according to the International Classification of Diseases, 10th revision (ICD-10), code M32. The incidence was calculated per 100,000 person-years. Findings from the result showed that the annual incidence of SLE decreased slightly from 5.42/100,000 person-years in 2005 to 3.6/100,000 person-years in 2015. This study however had a few limitations due to the use of the NHI database stem from the lack of accurate diagnosis. Second, the administrative claims data analyzed in this study were obtained when subjects visited healthcare institutions. Therefore, no information was available for SLE patients who did not visit a healthcare institution, which could underestimate the SLE burden.

Scolnik & Soriano (2016) conducted a systematic review aimed at determining the epidemiology of Lupus in Latin America. The study involved reviews based on publications found through searches of the MEDLINE and LILACS databases for relevant articles using the

combination search terms of lupus and (epidemiology, incidence, prevalence) and Latin America or each of the country names of the region. References within these selected reports were also reviewed. Findings from the study showed that out of the twelve studies were identified regarding the incidence or prevalence of SLE in Latin America. Incidence varied from 4.7 to 8.7/per/ 100000 person's years, and prevalence ranged from 47.6 to 90 per 100,000 inhabitants. There were important variations in the epidemiology of lupus in Latin America. These variabilities could be explained by genetic or environmental differences, differences in the methodology used, and/or in the quality of the studies. Latin America is heterogeneous and more regional studies are needed. Of the studies performed in Latin America, three were done in the Caribbean Islands, with populations that are small and with a different background than the majority of the subcontinent. Other six studies were done using a COPCORD methodology. This approach may not be the most adequate one to detect systemic diseases like lupus where not all the patients have joint involvement. Moreover, there is a selection bias in the respondents to the questionnaire. In the Argentinian study, incidence and prevalence of lupus were assessed in a health maintenance organization in Buenos Aires, but data cannot be extrapolated to the complete Argentinian population that has a greater proportion of mestizos.

Rees *et al*., (2017) conducted a systematic review aimed at determining the worldwide incidence and prevalence of SLE and variation with age, sex, ethnicity, and time. The author conducted a systematic search of MEDLINE and EMBASE search engines was carried out using Medical Subject Headings and keyword search terms for Systemic Lupus Erythematosus combined with incidence, prevalence, and epidemiology in August 2013 and updated in September 2016. Author, journal, year of publication, country, region, case-finding method, study period, number of incident or prevalent cases, incidence (per 100 000 person-years) or prevalence (per 100 000 persons) and age, sex, or ethnic group-specific incidence or prevalence were collected. The study findings showed that the highest estimates of incidence and prevalence of SLE were in North America [23.2/100 000 person-years (95% CI: 23.4, 24.0) and 241/100 000 people (95% CI: 130, 352), respectively]. The lowest incidences of SLE were reported in Africa and Ukraine (0.3/100 000 person-years), and the lowest prevalence was in Northern Australia (0 cases in a sample of 847 people). Women were more frequently affected than men for every age and ethnic group. Incidence peaked in middle adulthood and occurred later for men. People of Black ethnicity had the highest

incidence and prevalence of SLE, whereas those with White ethnicity had the lowest incidence and prevalence. There appeared to be an increasing trend of SLE prevalence with time.

Socio-demographic characteristics of individuals who have SLE

A study conducted by the CDC which was a funded population-based registry, to determine the prevalence and incidence of SLE among American Indian and Alaska Native people within the Indian Health Service clinical population (Ferucci *et al*., 2017). These studies overcame the shortcomings of previous epidemiologic data in the USA by using identical case definitions (meeting ≥4 American College of Rheumatology (ACR) criteria or a renal biopsy of lupus nephritis/end-stage renal disease or a rheumatologist's diagnosis), and a broad range of case-finding sources. The number of Hispanic and Asian patients in these three registries was small, so the CDC supported the creation of two similar lupus registries in California and New York. The recently published data from the California Lupus Surveillance Project (CLSP) and the Manhattan Lupus Surveillance Program (MLSP) included populations with greater numbers of Asian and Hispanic patients (Dall'Era *et al*., 2017; Izmirly *et al*., 2006). Both studies reported a higher prevalence and incidence rate of SLE in women compared with men, and in African Americans compared to Caucasians, similar to the data reported from Michigan and Georgia. The diverse population allowed estimation of incidence and prevalence among Hispanics and Asians, who had a higher incidence and prevalence of SLE compared to Caucasians, but lower than African Americans. The diverse populations included in these two registries allowed the first reliable estimates of incidence and prevalence among the Hispanic and Asian populations in the United States.

Eun Hui *et al*., (2020) carried out a study aimed at evaluating the trend of incidence and prevalence of systemic lupus erythematosus (SLE) in South Korea from 2005 to 2015. The study identified cases of SLE from the National Health Insurance Database, which records information on almost all Koreans. SLE was defined according to the International Classification of Diseases, 10th revision (ICD-10), code M32. The incidence was calculated per 100,000 person-years. Findings from the result showed that the peak age of incidence was 30 to 39 years in 2005; in 2015, the peak age of prevalence was 30 to 49 years and of incidence was 20 to 49 years

To study ethnic differences in the cardiovascular risk among patients with SLE, Barbhaiya, *et al*., (2017) analyzed Medicaid data from 2000 to 2010 and identified 65788 SLE patients- 93.1% were women and 42% were black, 38% were white, 16% were Hispanic, 3% were Asian, and 1% were American Indian/Alaska Native. The risk of cardiovascular events was increased among blacks (HR 1.14) compared to whites, while Hispanics and Asians had a lower risk of MI (HR 0.61 and HR 0.57, respectively). Blacks and Hispanics had a higher risk of stroke (HR 1.31 and HR 1.22, respectively).

Otsa *et al*., (2017) estimated the incidence and point prevalence of SLE in Estonia by extracting SLE ICD-10 codes for individuals older than 20 years of age from the Estonian Health Insurance Fund database. The reported SLE incidence in Estonia was lower than in countries with similar prevalence, presumably due to the use of a lower age limit of 20 years as a study inclusion criterion.

In southern Sweden, Ingvarsson *et al*. (2016) reported a decrease in the incidence rate of SLE over a period of 26 years, particularly in middle-aged women, while disease phenotype remained unchanged. The prevalence of SLE increased slowly over the same period. In Denmark, Hermanssen *et al*., (2016) in an analysis of the Danish National registry reported an incidence rate for SLE of 2.35 per 100,000. Sex-specific incidence rates of SLE and lupus nephritis peaked later in life among men than among women.

Yen *et al*., (2016) carried out a study with an aim to assess the Temporal Trends in SLE Mortality According to Sex, Race, Ethnicity, and Geographic Region in the United States over the Past Five Decades. The study measured temporal trends in age-standardized mortality rates (ASMR) for SLE and non-SLE causes by trend analysis using county-level data abstracted from the Centers for Disease Control and Prevention database. Findings from the study showed that SLE was listed as the primary cause of death in 50,249 individuals from 1968-2013 in the US with a peak crude mortality rate in the 1970s-80s and declined during the 2000s. Analysis of the trend in SLE case-fatality showed an overall decline in rates from 1999-2013. The average annual % change in SLE case-fatality ranged from -2.5% per year to -3.1% per year in various subpopulations during 1999-2013. With respect to race, age, and sex, the SLE mortality remained high in blacks (odds ratio 5.24, $p<0.001$). The higher SLE mortality in the general population was associated with female sex, however, analyses of case-fatality in different subpopulations revealed that in the SLE subpopulation, males had higher mortality (odds ratio 1.94,

p<0.001). The result findings also showed that the age histogram showed that the black died from SLE at a younger age than the whites with half (50%) of total death occurring by the age of 45 years in black versus age 59 years in whites, although the Hispanics died younger with half of the SLE deaths occurring by the age 44 years versus non-Hispanics by age 54 years.

Francis *et al*., (2018) estimated the incidence and prevalence of SLE in the population of Alberta, Canada, using administrative health data. Multiple population-based data sources, including the Alberta Health Care Insurance Plan Central Stakeholder Registry (AHCIP CSR), Fee-For-Service, and Hospital Discharge Abstract Database. Age- and sex-specific incidence and prevalence rates, and 95% confidence intervals (CI), were computed using the AHCIP CSR mid-year population estimates as the denominator, from 2000 to 2015. Findings from the study showed that the overall incidence of SLE for all age groups was 4.43 (95% CI 3.65, 5.04) per 100,000 population. The overall incidence in males and females of all age groups was 1.26 (95% CI 0.72, 1.76) and 7.69 (95% CI 6.22, 8.81) per 100,000 population, respectively. A prevalence of 47.99 per 100,000 (male = 13.5, female = 83.2) of SLE was observed for the year 2000 and has increased to 90 (male = 25.5, female = 156.7) per 100,000 population in 2015. Over the 16-year-period, the incidence of SLE in women was approximately six times higher than in men (odds ratio = 6.16). The highest and lowest incidence was recorded in 2001 and 2015, respectively. Despite the stable incidence of SLE, the findings of the study confirm that the prevalence of SLE has increased over the 16-year-period.

Case-mortality and morbidity from Systemic Lupus Erythematous (SLE)

Costenbader *et al*., (2015) analyzed Medicaid claims data and reported higher SLE mortality rates per 1000 patient-years among Native American (27.52), Caucasian (20.17), and African American (24.13) patients and were lower among Hispanic (7.12) or Asian (5.18) patients

Hermassen *et al*., (2017) in a nationwide, population-based cohort study demonstrated a significantly higher risk of myocardial infarction and cardiovascular mortality in SLE patients with lupus nephritis compared to SLE patients without lupus nephritis ((HR=18.3 vs

HR=2.2 for myocardial infarction and HR=7.8 vs HR=1.6 for cardiovascular mortality). The higher risk of stroke in SLE was not significantly affected by the presence of lupus nephritis.

Using data from the Swedish National Patient Register, Arkema, *et al*., (2017) studied the occurrence of ischemic and hemorrhagic stroke in patients with SLE. The relative risk of ischemic stroke in SLE was more than doubled compared with the general population (HR= 2.2), and importantly, the highest relative risks were observed within the first year after SLE diagnosis (HR=3.7).

Lee *et al*., (2016) performed a meta-analysis of studies examining all-cause and cause-specific standard mortality rates (SMR) in SLE. All-cause standard mortality rates were increased 2.6-fold in SLE patients. The risk of mortality was significantly increased for mortality due to renal disease (SMR 4.689), cardiovascular disease (SMR 2.253), and infection (SMR 4.980), but not due to cancer (SMR 1.163). In a retrospective cohort study carried out by Francis *et al*., (2016) using the UK Clinical Practice Research Datalink to estimate the mortality associated with SLE during the period 1999-2012 by age, gender, and region; and to ascertain the cause of death for people with SLE. The study reported that of the 2740 incident cases, 227 died, giving a mortality rate of 15.84/1000 person-years (95% CI 13.91, 18.04). This was 67% higher than in controls (MRR 1.67, 95% CI 1.43, 1.94, $P < 0.001$). Men with SLE had higher rates of mortality than females with SLE. Compared with controls, the mortality rate for males with SLE was 1.80 times that of male controls (95% CI 1.32, 2.45, $P < 0.001$); for females the mortality rate was 1.64 times higher (95% CI 1.37, 1.96, $P < 0.001$). The age-specific mortality rates increased significantly with age; however, the MRR diminished from 3.81 (95% CI 1.43, 10.14) in those aged <40 years to 0.82(95% CI 0.36, 1.83) in those ≥90years.

CHAPTER THREE
RESEARCH METHODOLOGY

3.1: Study Area

This study was carried out in Kingstown, Saint Vincent and the Grenadines. St. Vincent and The Grenadines comprises of 32 islands and cays, of which 9 are inhabited. The largest is St. Vincent (Mainland), where the nation's capital, Kingstown, is located. St. Vincent and the Grenadines has a population of approximately 111,000, which has remained fairly flat since 1990. In 2019, St Vincent and the Grenadines has an estimated population of 110,589. The country is densely populated with 307 people per square kilometer (792/sq. mi). The capital and largest city is Kingstown, with a population estimated at 35,000.

Most Vincentians are the descendants of African slaves brought to the region to farm plantations, as well as Portuguese and East Indians, who were brought to the island after slavery was abolished by the British living in the region. The largest ethnic group was African (66%), followed by those of mixed descent (19%), East Indian (6%), Europeans (mostly Portuguese (4%), and Carib Amerindian (2%). There is a growing community of Chinese people in the country. In 2012, the male population (55,551) outnumbered the female (53,637). The population is young, with almost 25 percent under the age of 15 and 41.7 percent under the age of 35. Although this under-35 age group has decreased since the 2001 census by 6.1 percent, it remains the largest proportion of the total population. The 2012 census determined the population aged under 5 years to be 8,645. A little over 9.1 percent of the population is over the age of 65.5.

A stable macroeconomic environment is a necessary condition for economic and social growth and development. The impact of the 2008 crisis has proven severe, with sharp decreases in official development funds, tourist arrivals, remittances, and foreign direct investment (FDI). The tourism sector, which had experienced a significant growth spurt up to 2008, reacted by contracting by 7.5 percent per annum, and other key sectors followed, resulting in spiking unemployment rates. SVG is also beleaguered by small domestic markets that constrain the efficiency and growth of the private sector; limited product diversification, increasing both the risk and the return that

can be derived from economic activity; and scale diseconomies in public service provision. The import of goods and services represented 57.9 percent of GDP in 2012 compared to 27.1 percent of exports during that same year. The past two decades represent years of economic transitioning for SVG as it moved from a largely agricultural-based economy towards growing reliance on services including real estate, transport, communication, storage, tourism-related businesses, and financial services. The development of the manufacturing sector has focused on metals, packaging, beverages, milling, and construction.

St Vincent has both public hospitals and private clinics in the area around Kingstown. Being a small developing nation, the level of care is well below that of the US or Europe and the public facilities are often stretched way beyond capacity.

There are public hospitals and clinics throughout the islands, with each place (except for Mayreau) having some form of a medical center. Any serious problems, however, will require a trip to St Vincent

Public spending on health in St Vincent and the Grenadines was four percent of GDP in 2011, equivalent to US$310 per capita. In the most recent survey, conducted between 1997 and 2010, there were 75 doctors, and 379 nurses and midwives per 100,000 people. Additionally, in the period 2007-12 virtually all births (99 percent) were attended by qualified health staff and in 2012, 94 percent of one-year-olds were immunized with one dose of measles (2012).

The Ministry of Health, Wellness and Environment manages planning and policy issues for health care. 40 health centers facilitate the delivery of primary care. Secondary care is offered at the Milton Cato Memorial Hospital in Kingstown and the six other hospitals in the country. A new wing at Milton Cato, built with the help of funding from the World Pediatrics Partnership and the Mustique Charitable Trust, acts as a center for pediatric surgery for St Vincent and the Grenadines and other nearby Caribbean nations. Serious medical problems often require air evacuation to the nearest large country with the necessary medical facilities. The government imports pharmaceuticals through the Pool Procurement Service of the Organization of Eastern Caribbean States (PPS/OECS) enabling it to

maximize the value of health care services to its citizens through the advantages of buying in bulk collectively, along with neighboring countries.

The Milton Cato Memorial Hospital (MCMH) is a 215-bed hospital serving the 110,000 inhabitants of St. Vincent and the Grenadines. The hospital was originally called the Colonial Hospital, built in the early 19th century by the British government under the colonial system, and later renamed Kingstown General Hospital. In the late 1800s, the Imperial Parliament granted permission for construction of a new wing, which was opened in 1889, and contained a total of seven beds. In 1914, the Princess Mary Louise wing was completed and used mainly as nurses' quarters.

The facility went through a variety of restructuring and refurbishment projects in the early 1900s, then, in 1994, two intensive care beds were established, bringing capacity to 211 beds. In 2002, Kingstown General became Milton Cato Memorial Hospital, in honor of Robert Milton Cato – the first Prime Minister of St. Vincent and the Grenadines when they gained independence from the British in 1979.

In December 2013, Milton Cato Memorial Hospital was severely water-damaged by a freak storm that flooded many areas of St. Vincent. Today, Milton Cato Memorial Hospital has approximately 600 employees, including doctors, nurses, technicians, and ancillary staff, who provide emergency, surgical, and medical care. In addition, the hospital often has visiting specialists from other countries.

As a public hospital, all of Milton Cato Memorial Hospital's services operate under the auspices of the Ministry of Health, Wellness and the Environment. Patients are required to pay user fees for medical services, which don't often recover the services' true costs. That being said, patients who cannot afford to pay are not prevented from accessing healthcare.

Meanwhile, healthcare on St. Vincent and the Grenadines has recently taken a giant leap forward with the July opening of the EC$42 million Modern Medical and Diagnostic Centre in Georgetown, the country's capital.

3.2: Study Design

The study utilized a retrospective population-based study that consists of secondary data derived from Milton Cato Memorial Hospital of patients with Autoimmune disease.

3.3.1: Inclusion Criteria

- Data on Immunological disease and rare disease

3.3.2: Exclusion

- Incomplete data on Immunological disease and rare disease

3.4: Data collection procedure

Data collection procedure

A semi-structured interviewer-administered questionnaire with close and open-ended questions will be used to collect relevant information with the aid of an android mobile device using the open data kit (ODK).

The interview schedule consisted of 15 sections:

A structured data extraction tool was employed to extract the data from the hospital record with the aid of an android mobile device using the open data kit (ODK). The data extraction tool was developed and modified with reference to existing tools used in similar studies. The data extraction tool comprises information on sociodemographic (age, sex), year of diagnosis, and diagnosis.

3.5: Outcome Measures and Data Analysis

For annual incidence, the year-specific numerator included subjects with incident cases of Autoimmune disease in the specific calendar year, and the denominator included the mid-year population from the Population and Demographic Health Survey (DHS) from 2013-

2019 which are cross-sectional surveys conducted every year, compiled by the Statistical Office Ministry of Finance, Economic Planning, Sustainable development and Information Technology of the Government of Saint Vincent and the Grenadines Population This nationally representative survey involved a multi-stage sampling design up to the household level with enumeration areas distributed by region and type of residence using the most recent national census as its sampling frame. Crude rates, sex- and age-specific rates, standardized rates adjusted for sex and age using the 2014-2018 mid-year population, and their 95% confidence intervals (CIs) were calculated.

Incident cases of autoimmune/immunological disease were defined as those without autoimmune/immunological disease in a particular year (e.g., 2014) and the preceding year (e.g., 2013 to 2014) that met the algorithm in that year (e.g., 2015) and the following year (e.g., 2016). Subgroup analyses were performed according to age and sex, The mortality rate in cases of Diabetes Mellitus Type 1 and Systemic Lupus Erythematous (SLE) was estimated by dividing the number of incident Diabetes Mellitus Type 1 and SLE cases who died during the study period by the number of person-years for the incident of Diabetes Mellitus Type 1 and SLE cases since diagnosis. Mortality rates were also stratified by time since diagnosis.

Data was being edited, collated, and entered into the 2016 Microsoft Excel Data Sheet, after which it was exported into the International Business Machine (IBM) Statistical Package for Social Sciences (SPSS) version 23.0 and R Studio statistical software for analysis. The analysis involved the calculation of descriptive statistics (such as frequency distributions, percentages, and means) and inferential statistics. Continuous variables were expressed as means ± standard deviation while categorical variables were expressed as absolute frequencies. Parametric analysis was used after tests for normality confirmed that continuous variables were normally distributed. The Chi-square test was used to test for association. All statistical tests were two-tailed and Level of Confidence was set at 95%, and P values < 0.05 were considered to be statistically significant.

Test of normality was done to check for normal distribution of data using the Shapiro-Wilk test and Kolmogorov-Smirnov test with a significance level set at 0.05. Assumptions were set that If the **Sig.** value of both Test ($p>0.05$), the data is normal. If it is below 0.05, the data significantly deviate from a normal distribution and non-parametric testing will be employed such as the median will be used instead of the mean to represent summative statistics due to the median is not affected by outliers or extreme values.

The information provided by the probability value (p-value) does not provide an estimate for the magnitude of the effect of interest and the precision of this magnitude (Nakagawa & Cuthill, 2007). As a result of this, most of the inferential statistics reported in this report did not only provide information on the p-value but also on the magnitude of the effect (effect size statistics) in the form of a correlation coefficient, regression coefficient, and also their confidence intervals (CIs). Confidence intervals (CIs) were interpreted as the value that encompasses the population or 'true' value. This style of reporting both the effect sizes and their CIs gave a clear understanding of the relationships between the variables (Nakagawa & Cuthill, 2007)

CHAPTER FOUR

RESULTS

4.1: Socio-demographics Characteristics of Patients

Variable	Frequency (n=347)	Percentage (%)
Age		
≤5	23	6.6
6-10	18	5.2
11-15	22	6.3
16-20	32	9.2
21-25	28	8.1
26-30	18	5.2
31-35	45	13.0
36-40	46	13.3
41-45	20	5.8
46-50	13	3.7
51-55	12	3.5
56-60	20	5.8
61-65	11	3.2
66-70	16	4.6
>70	23	6.6
Mean ± S.D (35.65 ± 21.16 yrs. old), 95% C.I for Mean (33.41-37.88), Median Age= 34 yrs. old		
Sex		
Male	129	37.2
Female	218	62.8
Year		
2014	103	29.7
2015	62	17.9
2016	104	30.0
2017	59	17.0
2018	19	5.4

S.D =Standard deviation, C.I= Confidence Interval

Table 4.1, shows the socio-demographic distribution of patients with autoimmune/immunological diseases with respect to age, sex. From 2014 to 2018, the total number of autoimmune/immunological cases seen in Milton Cato General Hospital was 347, with almost one-third 104(30%) occurring in the year 2016. Among the cases of autoimmune/immunological diseases the mean age was ***35.65 ± 21.16 years old*** and the ***median age= 34 years old,*** *almost two-third 218(62.6%) were females.*

Table 4.1a: Type of Autoimmune Diseases

Variable	Frequency (n=347)	Percentage (%)
Disease Type		
ADPKD	9	2.6
ARPKD	2	0.6
Autoimmune Hemolytic Anemia	2	0.6
Calciphylaxis	1	0.3
Charge Syndrome	1	0.3
Crohn Disease	1	0.3
Crohn Disease/Diabetes Type 2	1	0.3
Cryoglobulinemia	1	0.3
Diabetes Type 1	125	36.0
Diabetes Type 2/Pseudogout	1	0.3
Gout	11	3.2
Gout /Diabetes Type 2	1	0.3
Gout/Iridocyclitis	1	0.3
Human T- Lymphotropic Virus ***-1*** **(**HTLV-1)	1	0.3
Iridocyclitis	16	4.6
Iridocyclitis/Diabetes Type 2	2	0.6
Juvenile Arthritis	1	0.3
Kawasaki	5	1.4
Leukemia	1	0.3
Myasthenia Gravis	1	0.3
Unspecified Myopathy/Myositis	111	32.0
Unspecified Myopathy/Myositis/Diabetes Type 2	7	2.0
Pernicious Anemia	1	0.3
Pituitary Adenoma	2	0.6
Rheumatoid Arthritis	5	1.4
Sarcoidosis	1	0.3
Sjogren Syndrome	3	0.9
Systemic Lupus Erythematous (SLE)	26	7.5
SLE/Diabetes Mellitus/Type 2	1	0.3
Systemic Sclerosis	3	0.9
Ulcerative Colitis	3	0.9

ADPKD= Autosomal Dominant Polycystic Kidney Disease, ARPKD= Autosomal Recessive Polycystic

Table 4.1a shows that a greater percentage 125(36.0%) had diabetes Mellitus Type 1, 111(32.0%) had Unspecified myopathies, 26(7.5%) had SLE, only a few rare diseases were identified, this includes Charge disease 1(0.3%), Iridocyclitis 17(4.9%) and ARPKD 2(0.6%)

4.2: Incidence of autoimmune immunological diseases from 2014 -2018

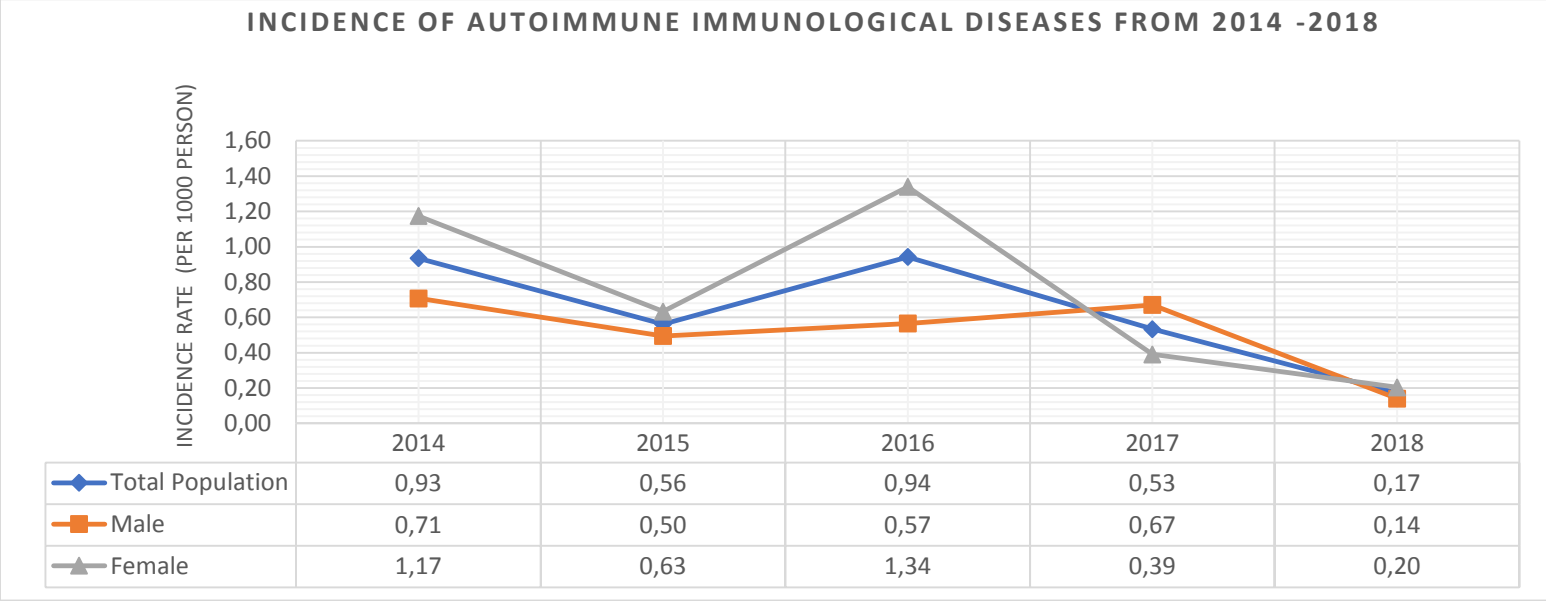
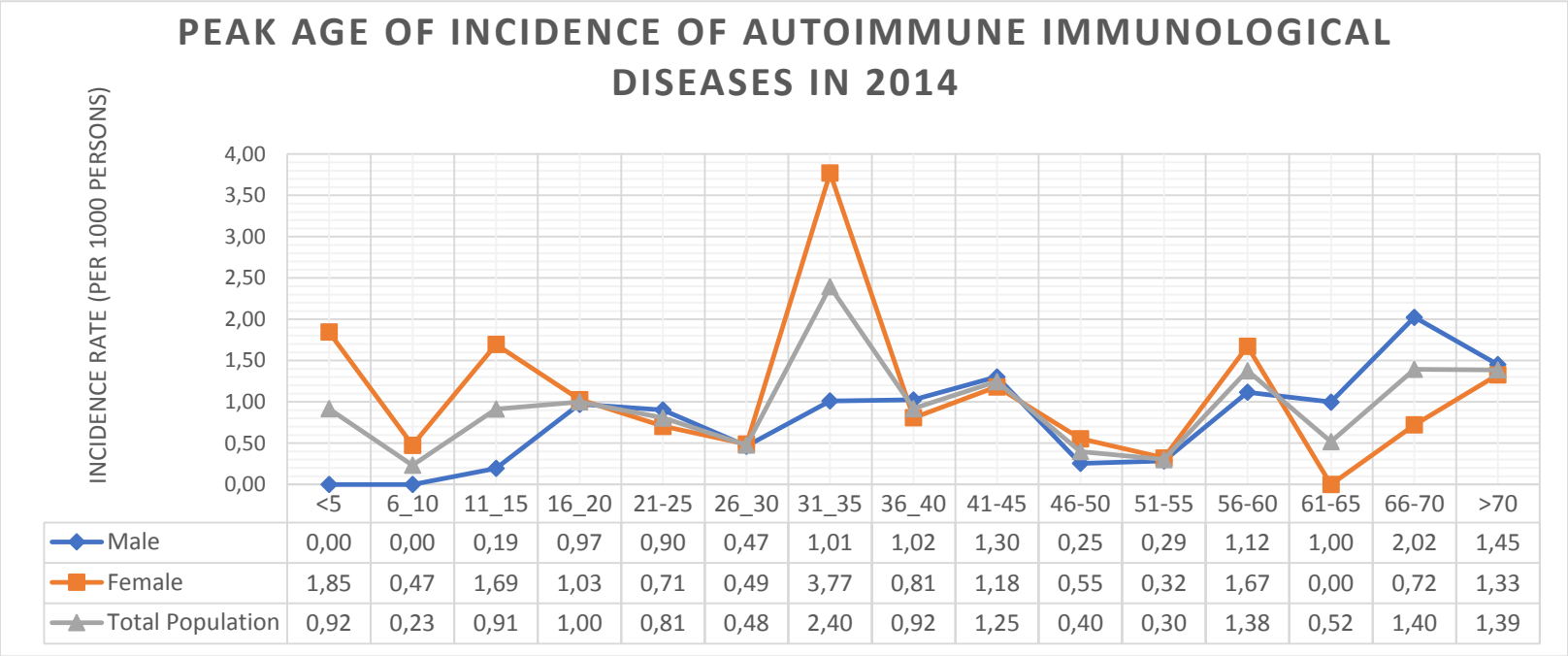


Fig 4.1: Incidence of autoimmune immunological diseases from 2014 -2018

Fig. 4.1 shows the trend in incidence by year. Every year, women showed a significantly higher incidence of autoimmune/immunological disease than men except in 2017 where the incidence for males was slightly higher than that of the females, there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2016 (0.94/1000 person-years). The lowest incidence was noted in 2018 (0.17/1000 person-years). Among sex, there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2014 for males (0.71/1000 person-years) and a peak incidence in 2016 for females (1.34/1000 person-years). The lowest incidence was noted in 2018 (0.14/1000 person-years) and (0.20/1000 person-years) for both male and female respectively.

4.2b: Peak Age of Incidence of autoimmune immunological diseases in 2014

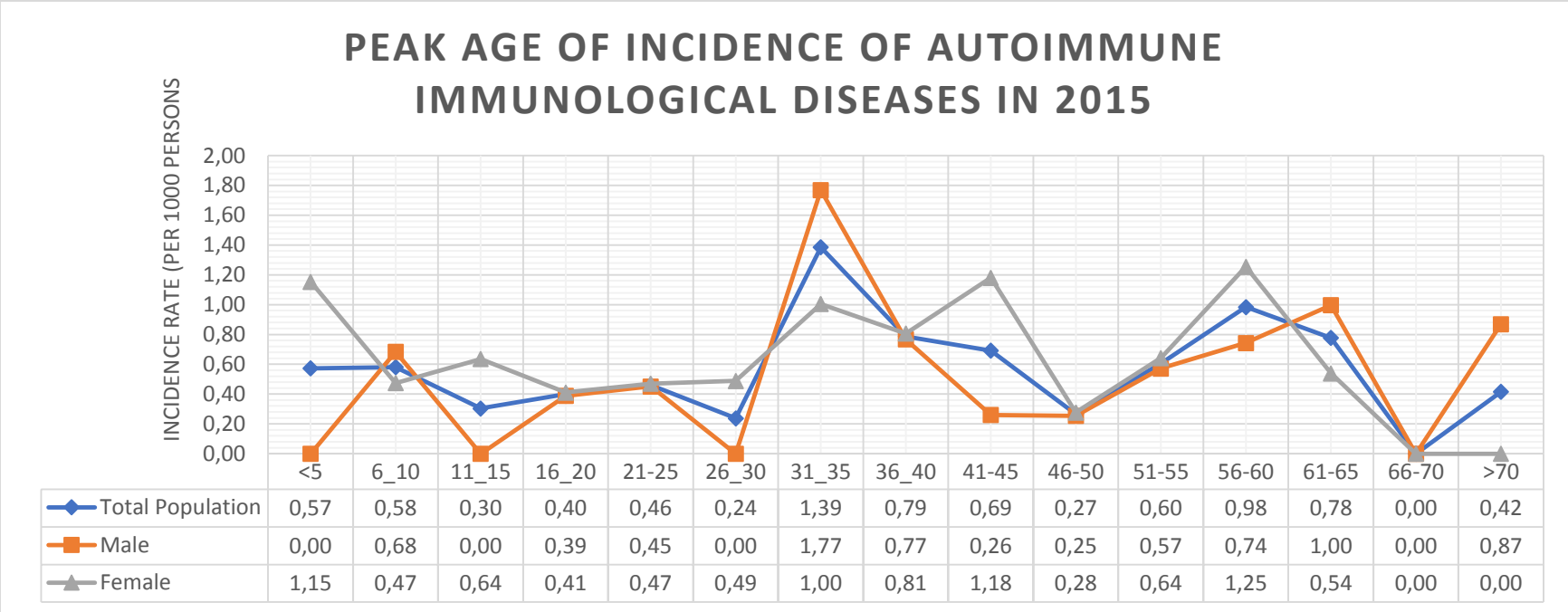


	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60	61-65	66-70	>70
Male	0,00	0,00	0,19	0,97	0,90	0,47	1,01	1,02	1,30	0,25	0,29	1,12	1,00	2,02	1,45
Female	1,85	0,47	1,69	1,03	0,71	0,49	3,77	0,81	1,18	0,55	0,32	1,67	0,00	0,72	1,33
Total Population	0,92	0,23	0,91	1,00	0,81	0,48	2,40	0,92	1,25	0,40	0,30	1,38	0,52	1,40	1,39

Fig 4.2: Peak Age of Incidence of autoimmune immunological diseases in 2014

Fig. 4.2 shows that the overall peak age of incidence was 31 to 35 years in 2014. In 2014, the peak age incidence among men was different > 70 years. However, the peak age of prevalence among women was similar to the overall incidence graph 31 to 35 years of age.

4.2c: Peak Age of Incidence of autoimmune immunological diseases in 2015

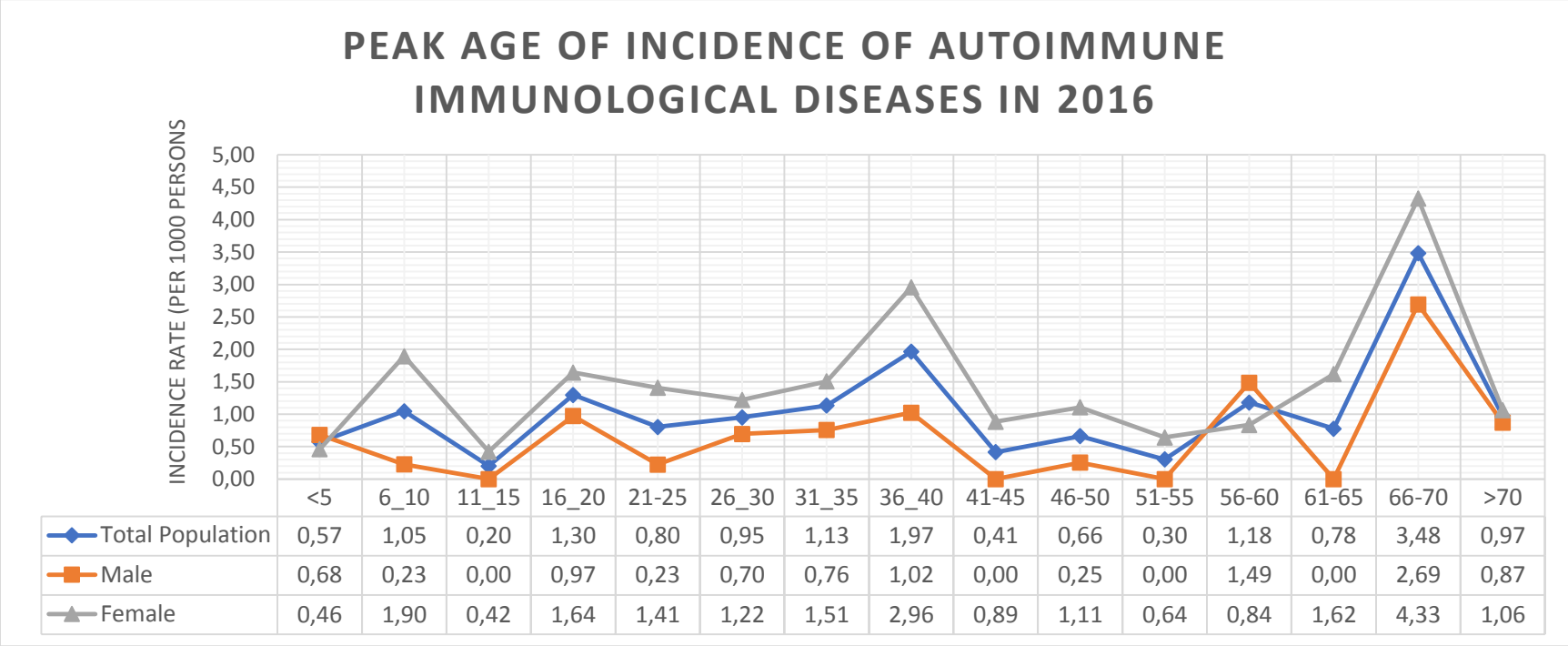


	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60	61-65	66-70	>70
Total Population	0,57	0,58	0,30	0,40	0,46	0,24	1,39	0,79	0,69	0,27	0,60	0,98	0,78	0,00	0,42
Male	0,00	0,68	0,00	0,39	0,45	0,00	1,77	0,77	0,26	0,25	0,57	0,74	1,00	0,00	0,87
Female	1,15	0,47	0,64	0,41	0,47	0,49	1,00	0,81	1,18	0,28	0,64	1,25	0,54	0,00	0,00

Fig 4.3: Peak Age of Incidence of autoimmune immunological diseases in 2015

Fig. 4.3 shows that the overall peak age of incidence was 31 to 35 years in 2015. In 2015, the peak age incidence among men was similar to the overall incidence graph 31 to 35 years of age. However, the peak age of prevalence among women was different (56-70) years of age to the overall incidence graph.

4.2d: Peak Age of Incidence of autoimmune immunological diseases in 2016

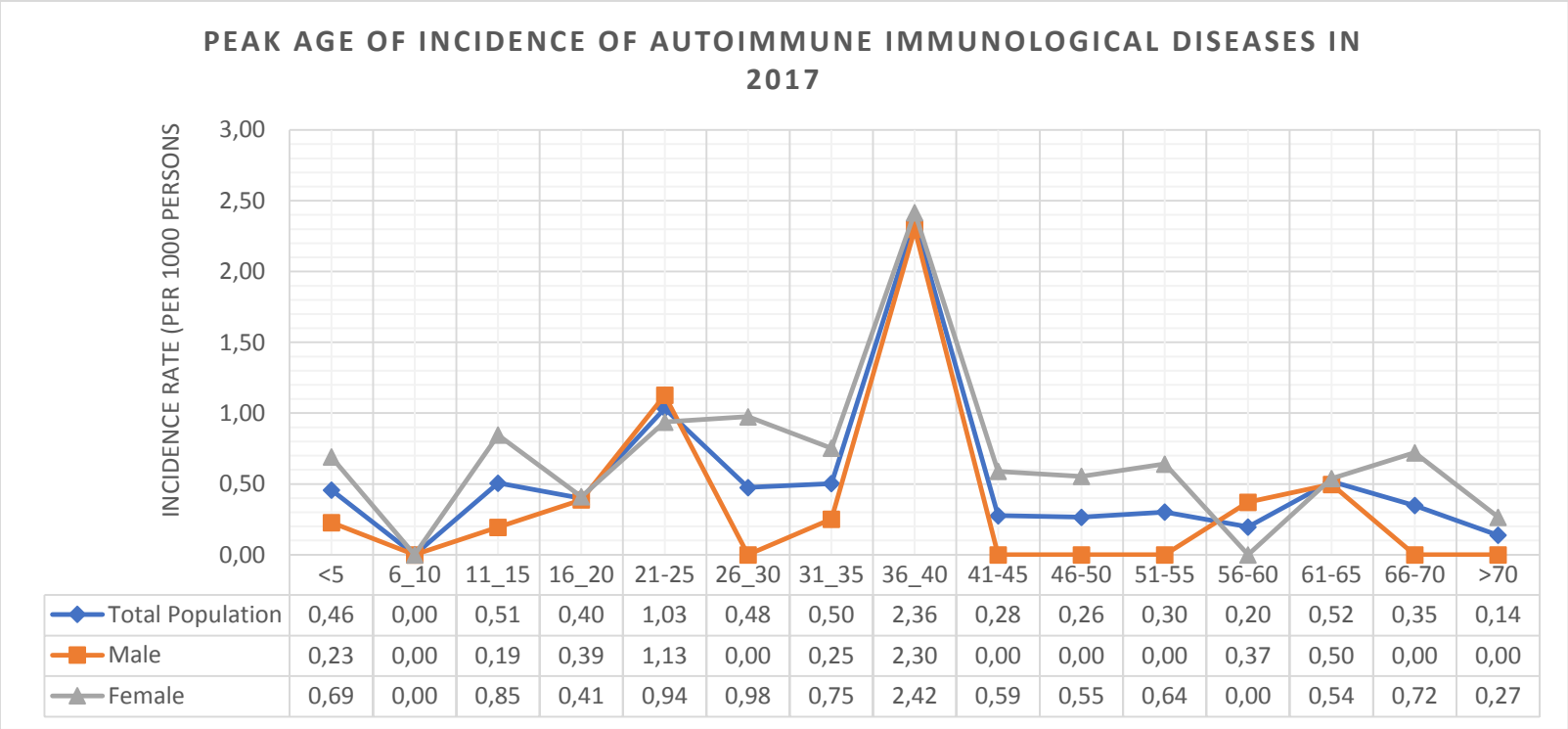


	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60	61-65	66-70	>70
Total Population	0,57	1,05	0,20	1,30	0,80	0,95	1,13	1,97	0,41	0,66	0,30	1,18	0,78	3,48	0,97
Male	0,68	0,23	0,00	0,97	0,23	0,70	0,76	1,02	0,00	0,25	0,00	1,49	0,00	2,69	0,87
Female	0,46	1,90	0,42	1,64	1,41	1,22	1,51	2,96	0,89	1,11	0,64	0,84	1,62	4,33	1,06

Fig 4.4: Peak Age of Incidence of autoimmune immunological diseases in 2016

Fig. 4.4 shows that the overall peak age of incidence was 66-70 years in 2016. In 2016, the peak age incidence among men and women was similar to the overall incidence graph 66-70years of age.

4.2e: Peak Age of Incidence of autoimmune immunological diseases in 2017

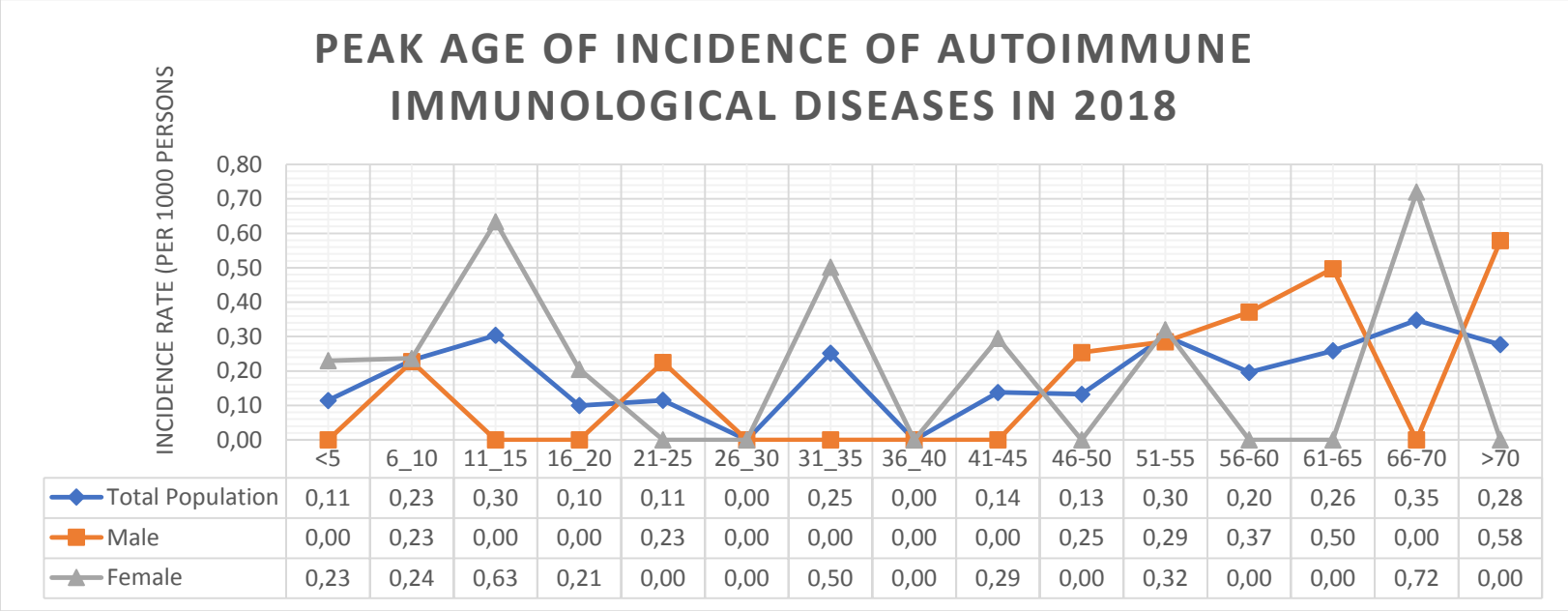


	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60	61-65	66-70	>70
Total Population	0,46	0,00	0,51	0,40	1,03	0,48	0,50	2,36	0,28	0,26	0,30	0,20	0,52	0,35	0,14
Male	0,23	0,00	0,19	0,39	1,13	0,00	0,25	2,30	0,00	0,00	0,00	0,37	0,50	0,00	0,00
Female	0,69	0,00	0,85	0,41	0,94	0,98	0,75	2,42	0,59	0,55	0,64	0,00	0,54	0,72	0,27

Fig 4.5: Peak Age of Incidence of autoimmune immunological diseases in 2017

Fig. 4.5 shows that the overall peak age of incidence was 36-40 to years in 2017. In 2017, the peak age incidence among men and women was similar to the overall incidence graph 36-40 years of age.

4.2f: Peak Age of Incidence of autoimmune immunological diseases in 2018



	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60	61-65	66-70	>70
Total Population	0,11	0,23	0,30	0,10	0,11	0,00	0,25	0,00	0,14	0,13	0,30	0,20	0,26	0,35	0,28
Male	0,00	0,23	0,00	0,00	0,23	0,00	0,00	0,00	0,00	0,25	0,29	0,37	0,50	0,00	0,58
Female	0,23	0,24	0,63	0,21	0,00	0,00	0,50	0,00	0,29	0,00	0,32	0,00	0,00	0,72	0,00

Fig 4.6: Peak Age of Incidence of autoimmune immunological diseases in 2018

Fig. 4.6 shows that the overall peak age of incidence was 66-70 years in 2018. In 2014, the peak age incidence among men was different > 70 years. However, the peak age of prevalence among women was similar to the overall incidence graph 66-70 years of age.

4.3 Association between Social demographic characteristics

Table 4.3a: Trend Analysis by Age group and Sex

Variable							df	χ2 (p-value)	*95% Confidence Interval (p-value)*	
Sex	**2014**	**2015**	**2016**	**2017**	**2018**					
	Freq (%)	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Total (%)**			**Lower Limit**	**Upper Limit**
Male	40(38.8)	28(45.2)	32(30.8)	21(35.6)	8(42.1)	129(37.2)				
Female	63(61.2)	34(54.8)	72(69.2)	38(64.4)	11(57.9)	218(62.8)	4	3.971 (0.423) [F]	0.371	0.475
Total	**103(100)**	**62(100)**	**104(100)**	**59(100)**	**19(100)**	**347(100**				
Age										
≤5	8(7.8)	5(8.1)	5(4.8)	4(6.8)	1(5.3)	23(6.6)	4	80.026 (0.000) [F*]	0.00	0.09
6-10	2(1.9)	5(8.1)	9(8.7)	0(0.0)	2(10.5)	18(5.2)				
11-15	9(8.7)	3(4.8)	2(1.9)	5(8.5)	3(15.8)	22(6.3)				
16-20	10(9.7)	4(6.5)	13(12.5)	4(6.8)	1(5.3)	32(9.2)				
21-25	7(25.0)	4(6.5)	7(6.7)	9(15.3)	1(5.3)	28(8.1)				
26-30	4(22.2)	2(3.2)	8(7.7)	4(6.8)	0(0)	18(5.2)				
31-35	19(42.2)	11(17.7)	9(8.7)	4(6.8)	2(10.5)	45(13.0)				
36-40	7(6.8)	6(9.7)	15(14.4)	18(30.5)	0(0.0)	46(13.3)				
41-45	9(8.7)	5(38.5)	3(2.9)	2(3.4)	1(5.3)	20(5.8)				
46-50	3(2.9)	2(3.2)	5(4.8)	2(3.4)	1(5.3)	13(3.7)				
51-55	2(1.9)	4(33.3)	2(1.9)	2(3.4)	2(10.5)	12(3.5)				
56-60	7(6.8)	5(25.0)	6(5.8)	1(1.7)	1(5.3)	20(5.8)				
61-65	2(1.9)	3(27.3)	3(2.9)	2(3.4)	1(5.3)	11(3.2)				
66-70	4(3.9)	0(0.0)	10(9.6)	1(1.7)	1(5.3)	16(4.6)				
>70	10(9.7)	3(4.8)	7(6.7)	1(1.7)	2(10.5)	23(6.6)				
Total	**103(100)**	**62(100)**	**104(100)**	**59(100)**	**19(100)**	**347(100**				

Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval) χ2= chi-square test statistics, df= degree of freedom.

In the table 43a, among sex, the females had higher proportions across the years (2014-2018) compared to that of the male we hereby fail to reject the null hypothesis which postulates that, ***there is no significant higher proportion of females to males who have autoimmune immunological disease from 2014 -2018 in Saint Vincent and the Grenadines*** due to there was no statistically significant association observed *(p>0.05).* Among the age group, those within the age group of 31-40 years had significantly higher proportions across the years (2014-2018) compared to that of other age groups, this difference was statistically significant *(p<0.05).*

Table 4.3b: Association between Social demographic characteristics

Variable	**Sex**			**df**	**χ2 (p-value)**	***95% Confidence Interval (p-value)***	
Sex	**Male**	**Female**					
	Freq (%)	**Freq (%)**	**Total (%)**			**Lower Limit**	**Upper Limit**
Age							
≤5	4(3.1)	19(8.7)	23(6.6)	14	24.861 (0.017) F*	0.04	0.31
6-10	5(3.9)	13(6.0)	18(5.2)				
11-15	2(1.6)	20(9.2)	22(6.3)				
16-20	14(10.9)	18(8.3)	32(9.2)				
21-25	13(10.1)	15(6.9)	28(8.1)				
26-30	5(3.9)	13(6.0)	18(5.2)				
31-35	15(11.6)	30(13.8)	45(13.0)				
36-40	20(15.5)	26(11.9)	46(13.3)				
41-45	6(4.7)	14(6.4)	20(5.8)				
46-50	4(3.1)	9(4.1)	13(3.7)				
51-55	4(3.1)	8(3.7)	12(3.5)				
56-60	11(8.5)	9(4.1)	20(5.8)				
61-65	6(4.7)	5(2.3)	11(3.2)				
66-70	7(5.4)	9(4.1)	16(4.6)				
>70	13(10.1)	10(4.6)	23(6.6)				
Total	**129(100)**	**218(100)**	**347(100)**				

Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval) χ2= chi-square test statistics, df= degree of freedom.

In table 4.3b, A statistically significant association was observed between Age and Sex, those within the age group of 36-40 years had significantly higher proportions of both males and females compared to that of other age groups, this difference was statistically significant *(p<0.05).*

4.4: Socio-demographics Characteristics of Patients with Diabetes Mellitus Type 1

Table 4.4: **Socio-demographics Characteristics of Patients with Diabetes Mellitus Type 1**

Variable	**Frequency (n=125)**	**Percentage (%)**
Age		
≤5	9	7.2
6-10	7	5.6
11-15	12	9.6
16-20	10	8.0
21-25	14	11.2
26-30	9	7.2
31-35	28	22.4
36-40	34	27.2
>40	2	1.6
Mean ± S.D (26.58 ± 11.73) yrs. old, 95% C.I for Mean (24.50-28.65), Median Age= 31 yrs. old		
Sex		
Male	44	35.2
Female	81	64.8
Year		

2014	38	30.4
2015	25	20.0
2016	23	18.4
2017	36	28.8
2018	3	2.4

S.D=Standard deviation, C.I= Confidence Interval

Table 4.1, shows the socio-demographic distribution of patients with Diabetes Mellitus Type 1 with respect to age, sex. From 2014 to 2018, the total number of cases of Diabetes Mellitus Type 1 in Milton Cato General Hospital was 125, with almost one-third 38(30.4%) occurring in the year 2014. Among the cases of Diabetes Mellitus Type 1 the mean age was ***26.58 ± 11.73yrs old*** and the ***median age= 31 yrs old, more than two-third 81(64.8%) were females.***

4.5: Incidence of Diabetes Mellitus Type 1 from 2014 -2018

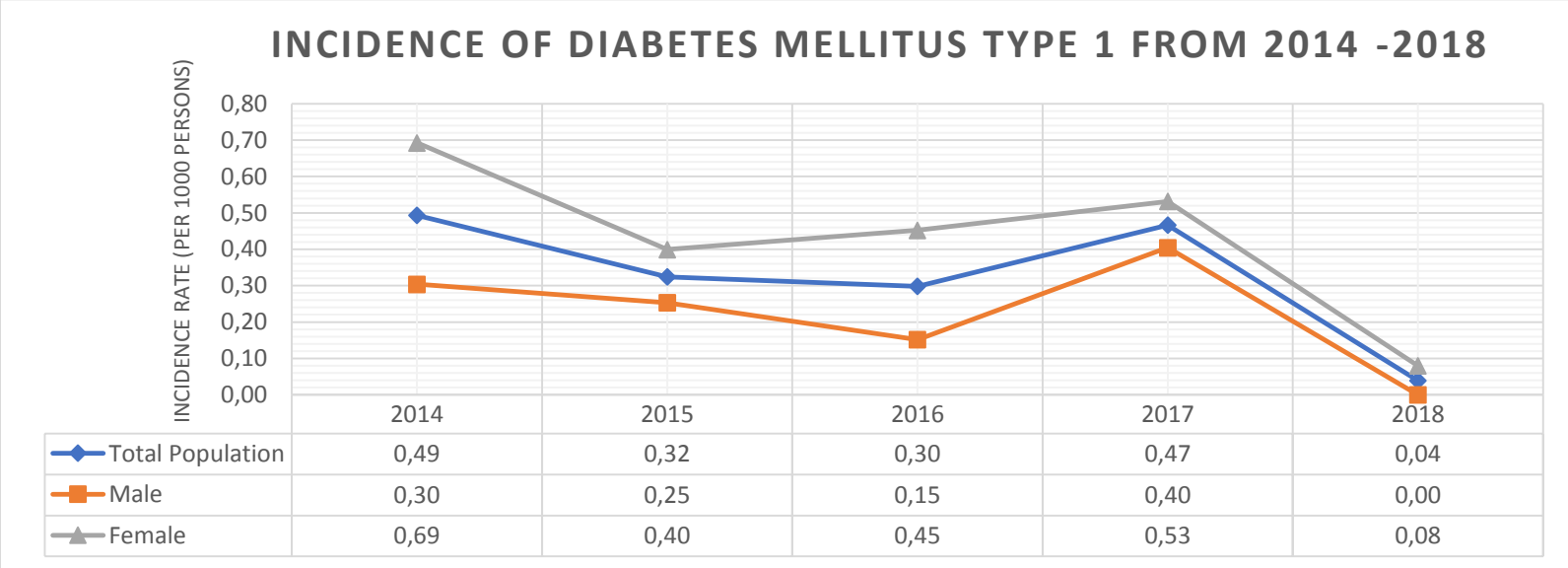
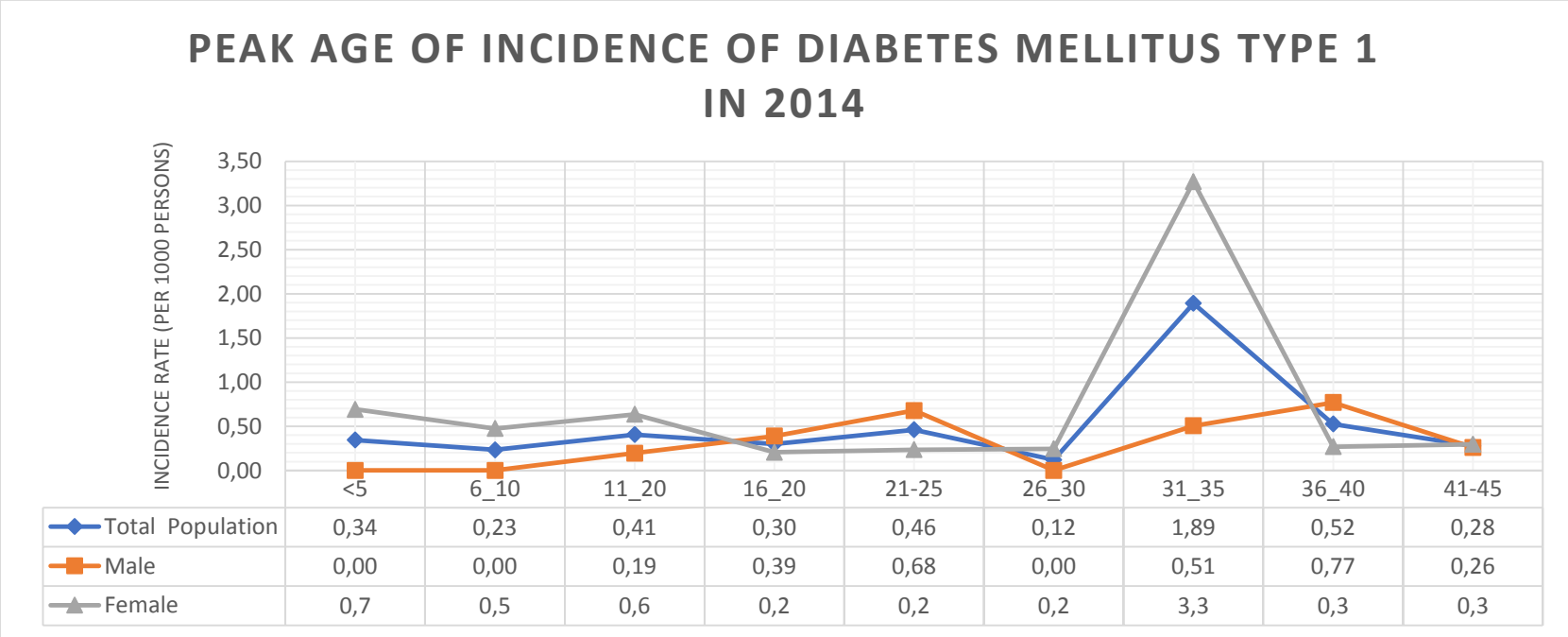


Fig 4.7: Incidence of Diabetes Mellitus Type 1 from 2014 -2018

Fig. 4.7 shows the trend in incidence by year. Every year, women showed a significantly higher incidence of Diabetes Mellitus Type 1 than men, there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2014 (0.49/1000 person-years). The lowest incidence was noted in 2018 (0.04/1000 person-years). Among sex, there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2017 for males (0.40/1000 person-years) and a peak incidence in 2014 for females (0.69/1000 person-years). The lowest incidence was noted in 2018 (0.00/1000 person-years) and (0.08/1000 person-years) for both male and female respectively.

4.5b: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2014

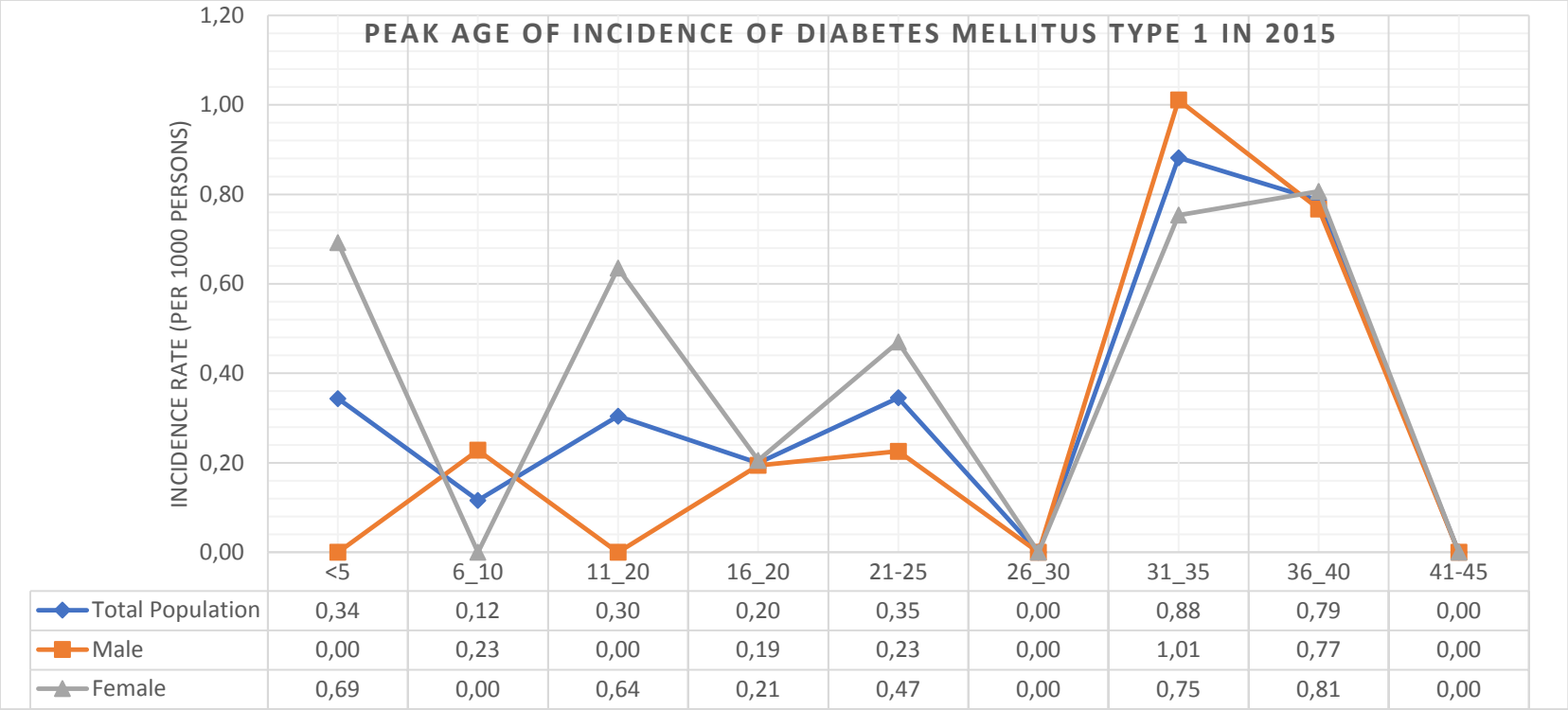


	<5	6_10	11_20	16_20	21-25	26_30	31_35	36_40	41-45
Total Population	0,34	0,23	0,41	0,30	0,46	0,12	1,89	0,52	0,28
Male	0,00	0,00	0,19	0,39	0,68	0,00	0,51	0,77	0,26
Female	0,7	0,5	0,6	0,2	0,2	0,2	3,3	0,3	0,3

Fig 4.8: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2014

Fig. 4.8 shows that the overall peak age of incidence was 31 to 35 years in 2014. In 2014, the peak age incidence among men was different 36-40 years. However, the peak age of prevalence among women was similar to the overall incidence graph 31 to 35 years of age.

4.5c: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2015



	<5	6_10	11_20	16_20	21-25	26_30	31_35	36_40	41-45
Total Population	0,34	0,12	0,30	0,20	0,35	0,00	0,88	0,79	0,00
Male	0,00	0,23	0,00	0,19	0,23	0,00	1,01	0,77	0,00
Female	0,69	0,00	0,64	0,21	0,47	0,00	0,75	0,81	0,00

Fig 4.9: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2015

Fig. 4.9 shows that the overall peak age of incidence was 36 to 40 years in 2015. In 2015, the peak age incidence among men and women similar to the overall incidence graph 36 to 40 years of age.

4.5d: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2016

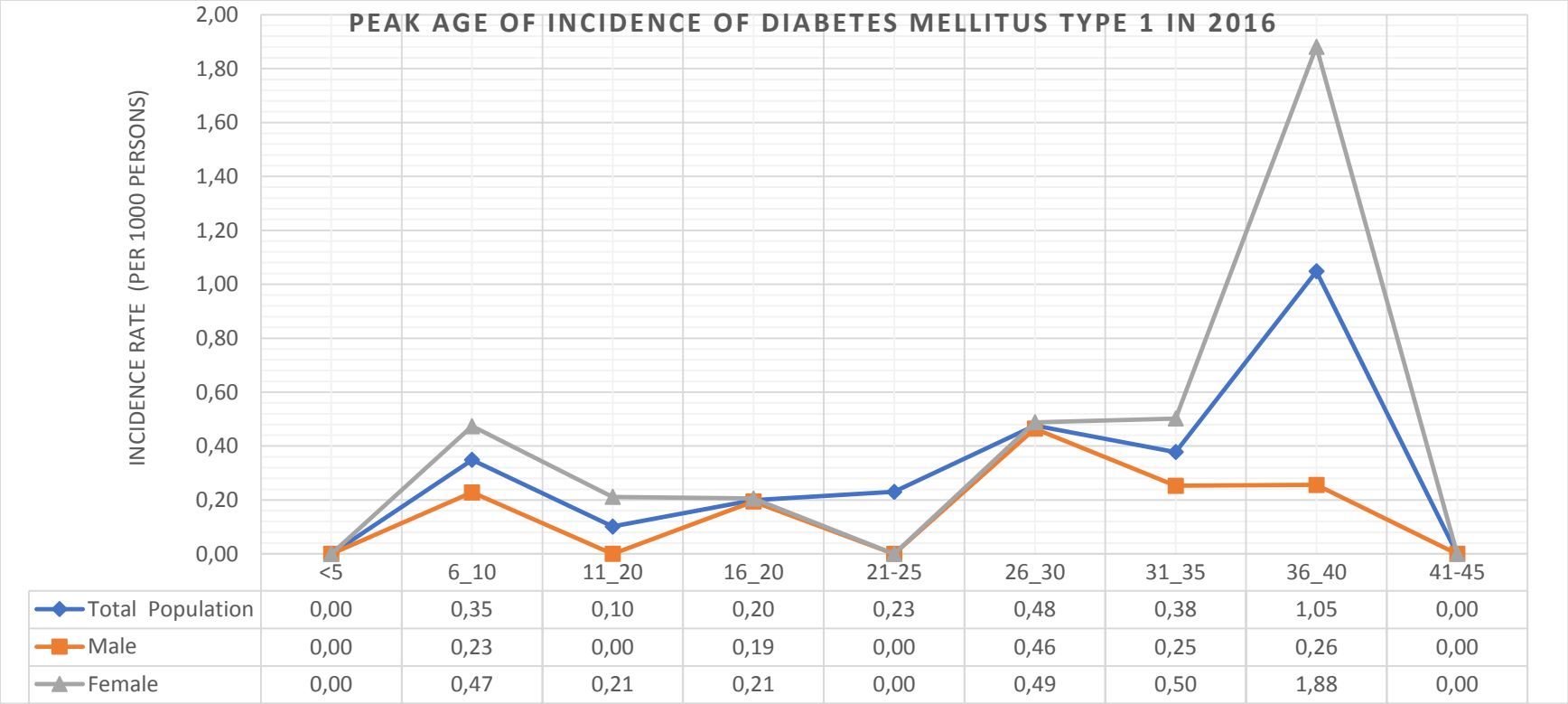
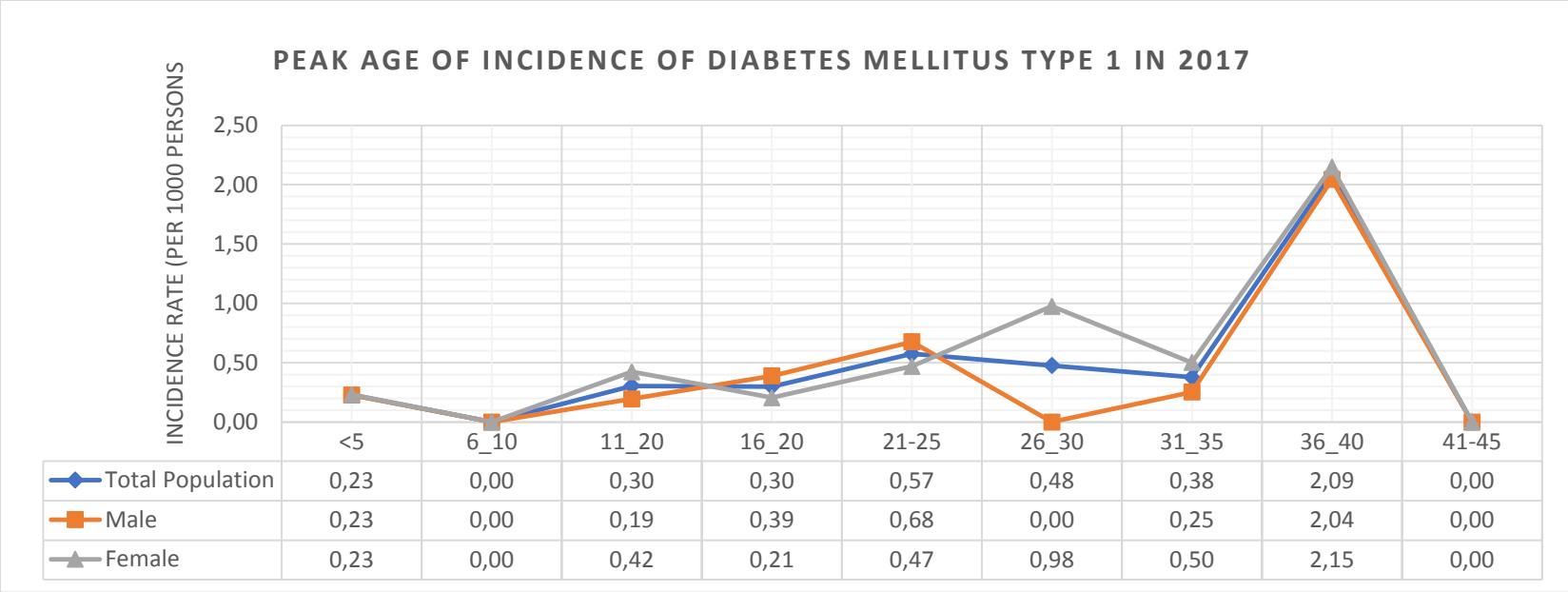


Fig 4.10: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2016

Fig. 4.10 shows that the overall peak age of incidence was 36 to 40 years in 2016. In 2016, the peak age incidence among men was different 26-30 years. However, the peak age of prevalence among women was similar to the overall incidence graph 36-40 years of age.

4.5e: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2017

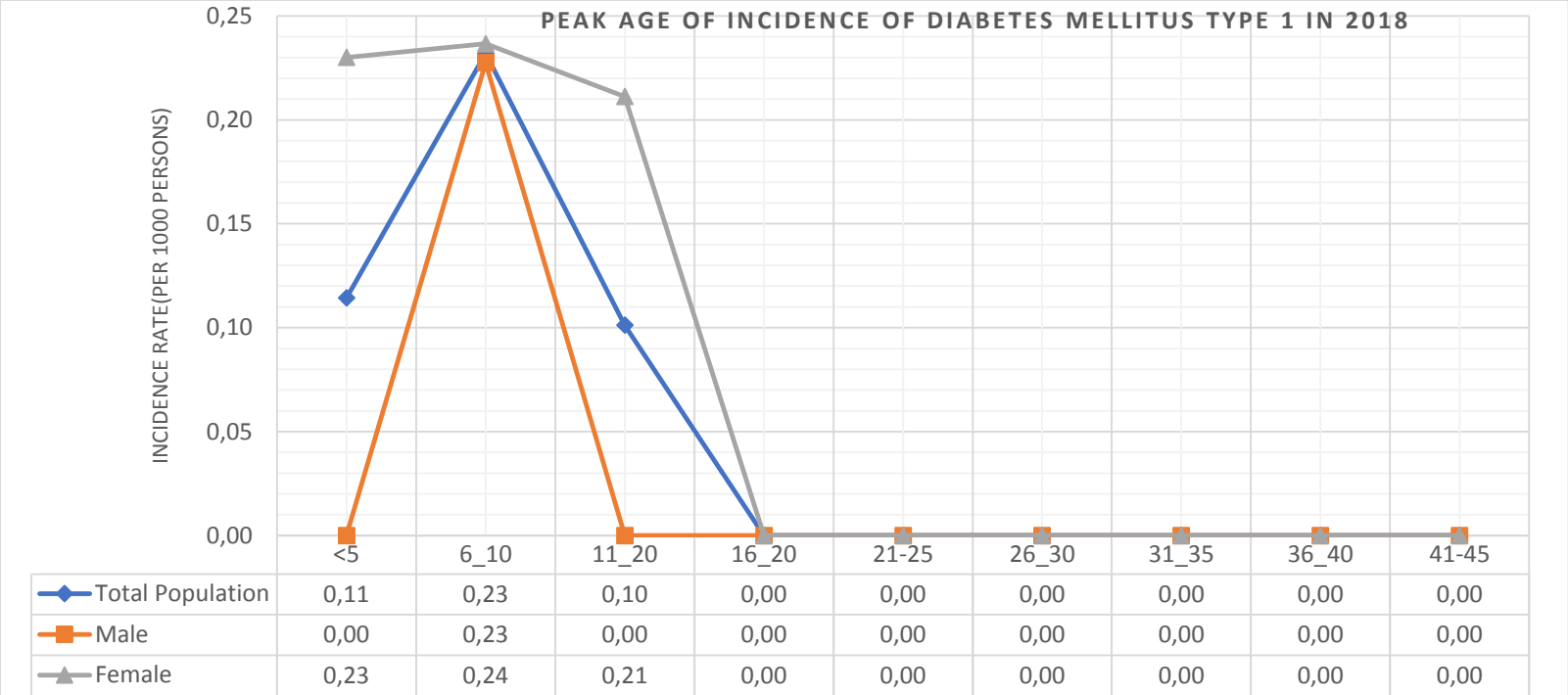


	<5	6_10	11_20	16_20	21-25	26_30	31_35	36_40	41-45
Total Population	0,23	0,00	0,30	0,30	0,57	0,48	0,38	2,09	0,00
Male	0,23	0,00	0,19	0,39	0,68	0,00	0,25	2,04	0,00
Female	0,23	0,00	0,42	0,21	0,47	0,98	0,50	2,15	0,00

Fig 4.11: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2017

Fig. 4.11 shows that the overall peak age of incidence was 36 to 40 years in 2017. In 2017, the peak age incidence among men and women was similar to the overall incidence graph 36-40 years of age.

4.5f: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2018



	<5	6_10	11_20	16_20	21-25	26_30	31_35	36_40	41-45
Total Population	0,11	0,23	0,10	0,00	0,00	0,00	0,00	0,00	0,00
Male	0,00	0,23	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Female	0,23	0,24	0,21	0,00	0,00	0,00	0,00	0,00	0,00

Fig 4.12: Peak Age of Incidence of Diabetes Mellitus Type 1 in 2018

Fig. 4.12 shows that the overall peak age of incidence was 6-10 years in 2018. In 2018, the peak age incidence among men and women was similar to the overall incidence graph 6-10 years of age.

4.6 Association between Social demographic characteristics

Table 4.6a: Trend Analysis by Age group and Sex

Variable							df	χ2 (p-value)	*95% Confidence Interval (p-value)*	
Sex	**2014**	**2015**	**2016**	**2017**	**2018**					
	Freq (%)	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Total (%)**			**Lower Limit**	**Upper Limit**
Male	12(31.6)	10(22.7)	6(26.1)	16(44.4)	0(0.)	44(35.2)				
Female	26(68.4)	15(60.0)	17(73.9)	20(55.6)	3(100.0)	81(64.8)	4	3.783 (0.392) F	0.308	0.476
Total	**38(100)**	**25(100)**	**23(100)**	**36(100)**	**3(2.4)**	**125(100)**				
Age										
≤5	3(7.9)	3(12.0)	0(0.0)	2(5.6)	1(33.3)	9(7.2)	32	0.088 (0.708) F	0.308	0.476
6-10	2(5.3)	1(4.0)	3(13.0)	0(0.0)	1(33.3)	7(5.6)				
11-15	4(10.5)	3(12.0)	1(4.3)	3(8.3)	1(33.3)	12(9.6)				
16-20	3(7.9)	2(8.0)	2(8.7)	3(8.3)	0(0.0)	10(8.0)				
21-25	4(10.5)	3(12.0)	2(8.7)	5(13.9)	0(0.0)	14(11.2)				
26-30	1(2.6)	0(0.0)	4(17.4)	4(11.1)	0(0.0)	9(7.2)				
31-35	15(39.5)	7(28.0)	3(13.0)	3(8.3)	0(0.0)	28(22.4)				
36-40	4(11.8)	6(24.0)	8(34.8)	16(44.4)	0(0.0)	24(27.2)				
>40	2(5.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(1.6)				
Total	**38(100)**	**25(100)**	**23(100)**	**36(100)**	**3(2.4)**	**125(100)**				

Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval) χ2= chi-square test statistics, df= degree of freedom.

In the table 4.6a, among sex, the females had higher proportions across the years (2014-2018) compared to that of the male we hereby fail to reject the null hypothesis which postulates that, ***there is no significant higher proportion of females to males who have Diabetes Mellitus Type 1 from 2014 -2018 in Saint Vincent and the Grenadines*** due to there was no statistically significant association observed

(p>0.05). Among the age group, those within the age group of 31-40 years had significantly higher proportions across the years (2014-2018) compared to that of other age groups, this difference was not statistically significant *(p>0.05).* We hereby fail to reject the null hypothesis which postulates that ***there is no significant higher proportion of individuals ≤ 20 years of age compared to other age groups who have Diabetes Mellitus Type 1 from 2014 -2018 in Saint Vincent and the Grenadines.***

Table 4.6b: Association between Social demographic characteristics

Variable	**Sex**			**df**	**χ2 (p-value)**	***95% Confidence Interval (p-value)***	
Sex	**Male**	**Female**					
	Freq (%)	**Freq (%)**	**Total (%)**			**Lower Limit**	**Upper Limit**
Age							
≤5	1(2.3)	8(9.9)	9(7.2)	8	10.632 (0.231) F*	0.158	0.303
6-10	2(4.5)	5(6.2)	7(5.6)				
11-15	2(4.5)	10(12.3)	12(9.6)				
16-20	6(13.6)	4(4.9)	10(8.0)				
21-25	7(15.9)	7(8.6)	14(11.2)				
26-30	2(4.5)	7(8.6)	9(7.2)				
31-35	8(18.2)	20(24.7)	28(22.4)				
36-40	15(34.1)	19(23.5)	34(27.2)				
>40	1(2.3)	1(1.2)	9(1.6)				
Total	**44(100)**	**81(100)**	**125(100)**				

****Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval) χ2= chi-square test statistics, df= degree of freedom.***

In the table 4.6b, those within the age group of 36-40 years had higher proportions of both male and female compared to that of other age groups to having diabetics mellitus type 1, however, there was no statistically significant association observed between age and sex *(p>0.05)*

4.6c: Case-mortality from Diabetes Mellitus Type 1 from 2014 -2018

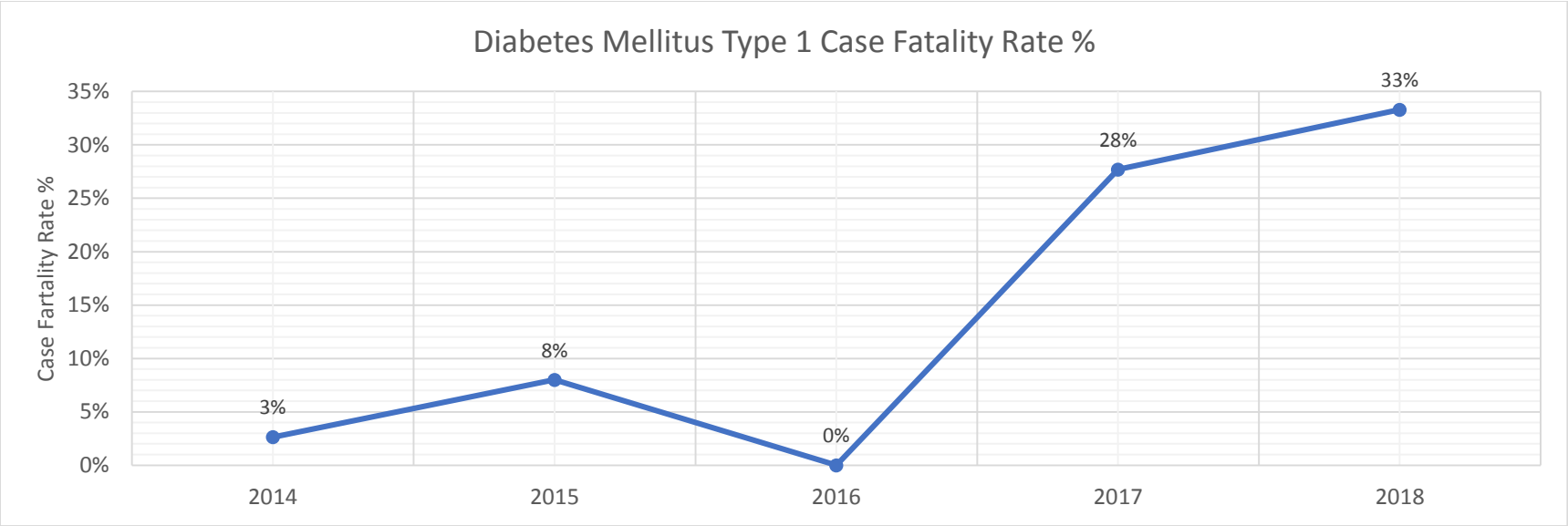


Fig 4.13 shows the case fatality from Diabetics Mellitus Type 1 of the total, 2018 had the highest case fatality of 33% compared to the other years with 2016 having no case fatality at all.

4.7: Socio-demographics Characteristics of Patients with Unspecified Myositis/Myopathies

Table 4.7: Socio-demographics Characteristics of Patients with Unspecified Myositis/Myopathies

Variable	Frequency (n=118)	Percentage (%)
Age		
≤10	14	11.9
11-20	20	16.9
21-30	11	9.3
31-40	14	11.9
41-50	11	9.3
51-60	18	15.3
61-70	14	11.9
71-80	9	7.6
>80	7	5.9
Mean ± S.D (41.66 ± 24.86) yrs. old, 95% C.I for Mean (37.13-46.19), Median Age = 40.50 yrs. old		
Sex		
Male	54	45.8
Female	64	54.2
Comorbidity		
Yes	7	5.9
No	111	94.1
Year		
2014	46	39.0
2015	20	16.9
2016	49	41.5
2017	0	0.0
2018	3	2.5

S. D=Standard deviation, C. I= Confidence Interval

Table 4.7, shows the socio-demographic distribution of patients with Unspecified Myositis/Myopathies with respect to age, sex. From 2014 to 2018, the total number of cases of Unspecified Myositis/Myopathies in Milton Cato General Hospital was 118, with more than one-third 46(39.0%) occurring in the year 2014. Among the cases of Unspecified Myositis/Myopathies, the mean age was ***41.66 ± 24.86*** and the ***median Age= 40.50 yrs old, more than half 64(54.2%) were females.*** **Only a few, 7(5.9%) had co-morbidity, with the morbidity been diabetes mellitus type 2.**

4.8 Incidence of Unspecified Myositis/Myopathies from 2014 -2018

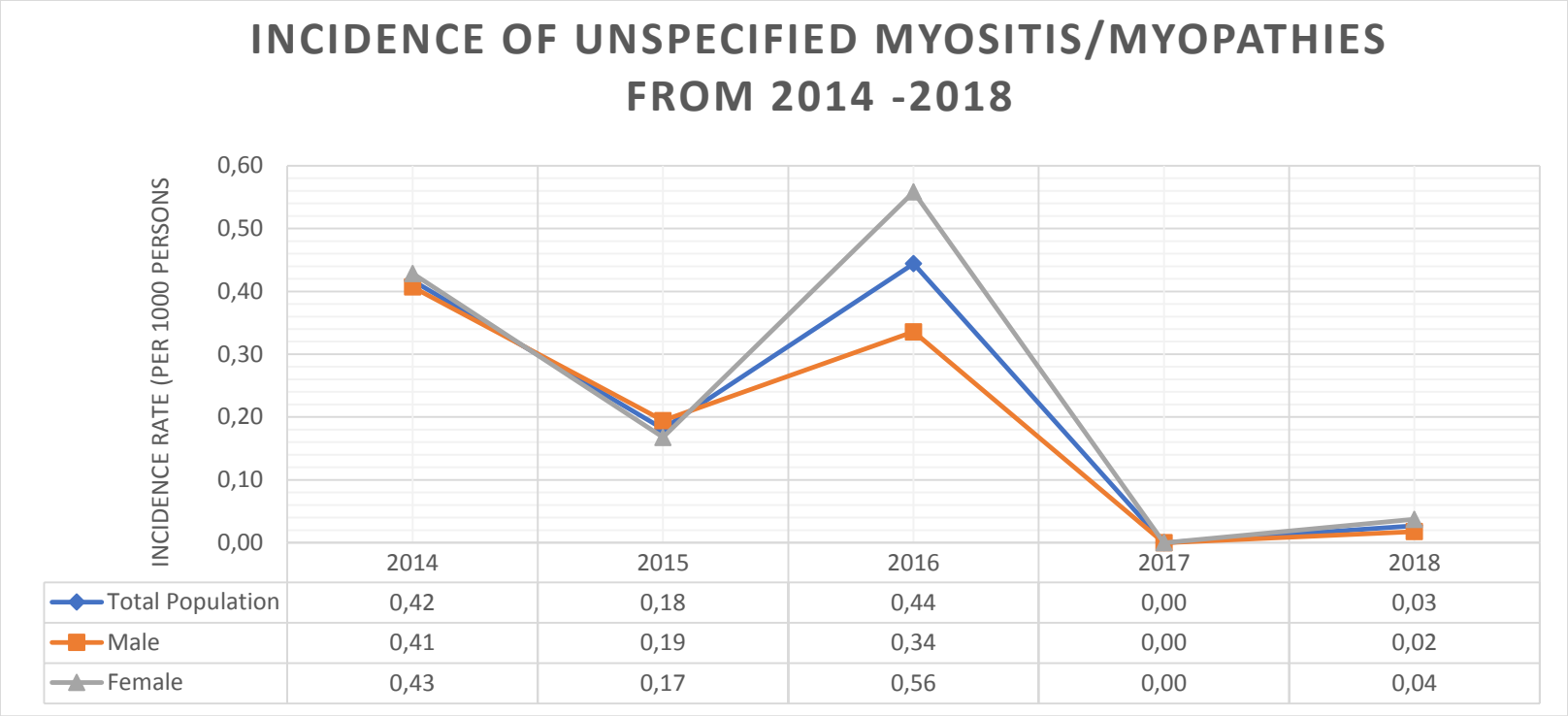


Fig 4.14: Incidence of Unspecified Myositis/Myopathies from 2014 -2018

Fig. 4.14: shows the trend in incidence by year. Every year, women showed a significantly higher incidence of Unspecified Myositis/Myopathies than men except in 2015 where the incidence for males was slightly higher than that of the females, there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2016 (0.44/1000 person-years). The lowest incidence was noted in 2018 (0.03/1000 person-years). Among sex, there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2014 for males (0.41/1000 person-years) and a peak incidence in 2016 for females (0.56/1000 person-years). The lowest incidence was noted in 2018 (0.02/1000 person-years) and (0.04./1000 person-years) for both male and female respectively.

4.8a: Peak Age of Incidence of in 2014 Unspecified Myositis/Myopathies

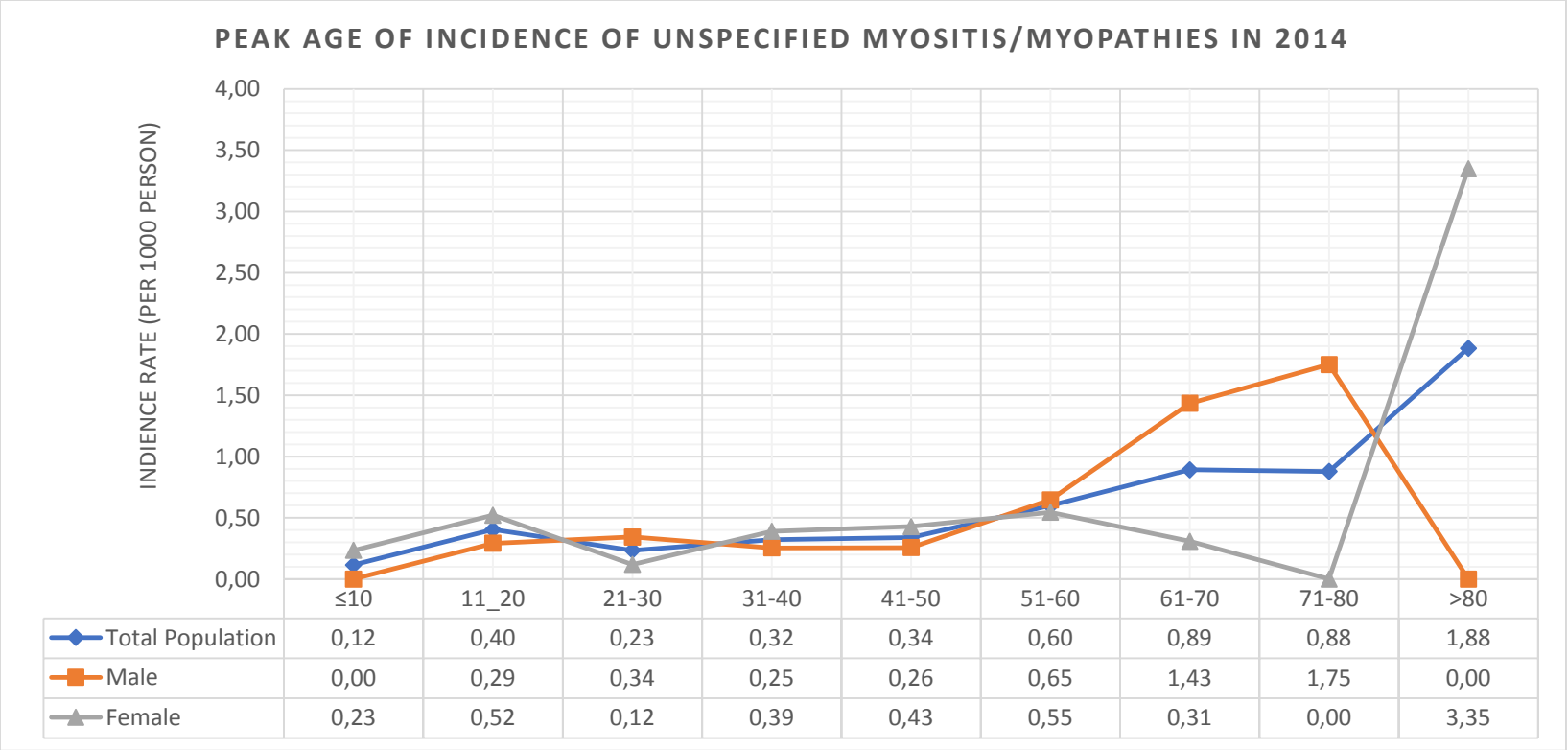


Fig 4.15: Peak Age of Incidence of Unspecified Myositis/Myopathies in 2014

Fig. 4.15 shows that the overall peak age of incidence was >80 years in 2014. In 2014, the peak age incidence among men was different 71-80 years. However, the peak age of prevalence among women was similar to the overall incidence graph >80 years of age.

4.8b: Peak Age of Incidence of Unspecified Myositis/Myopathies in 2015

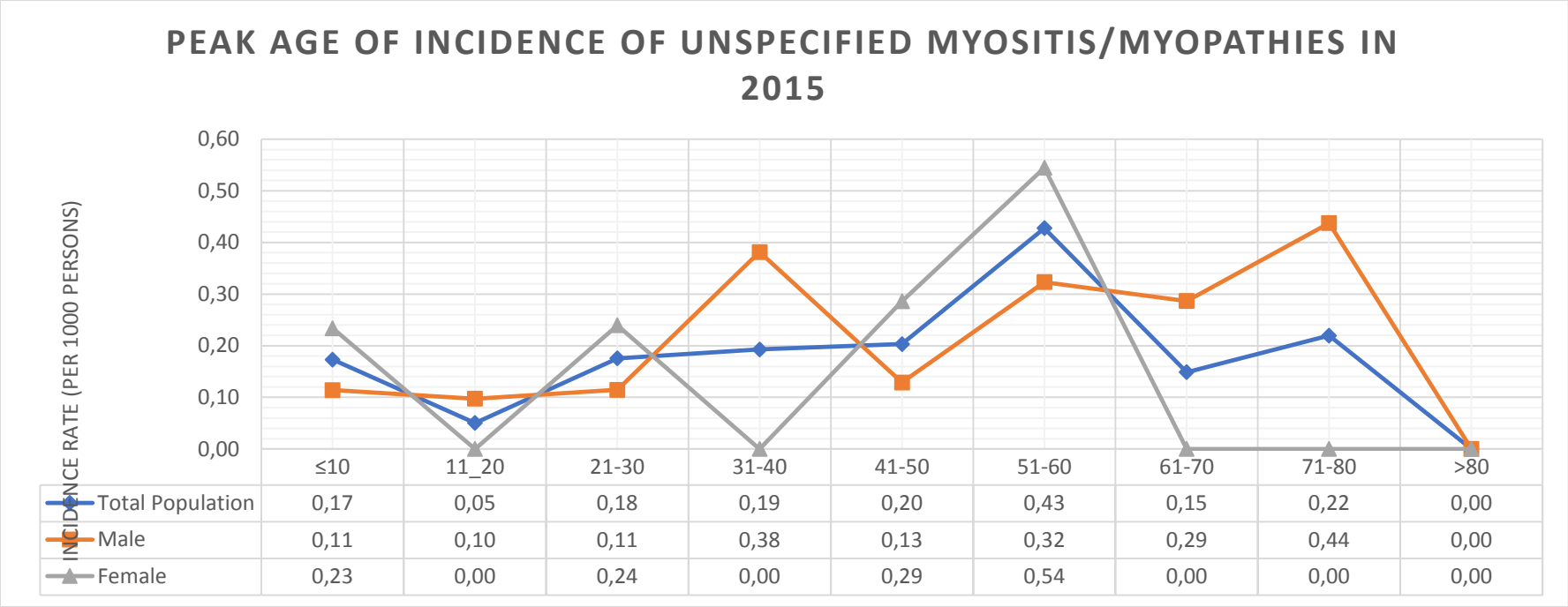
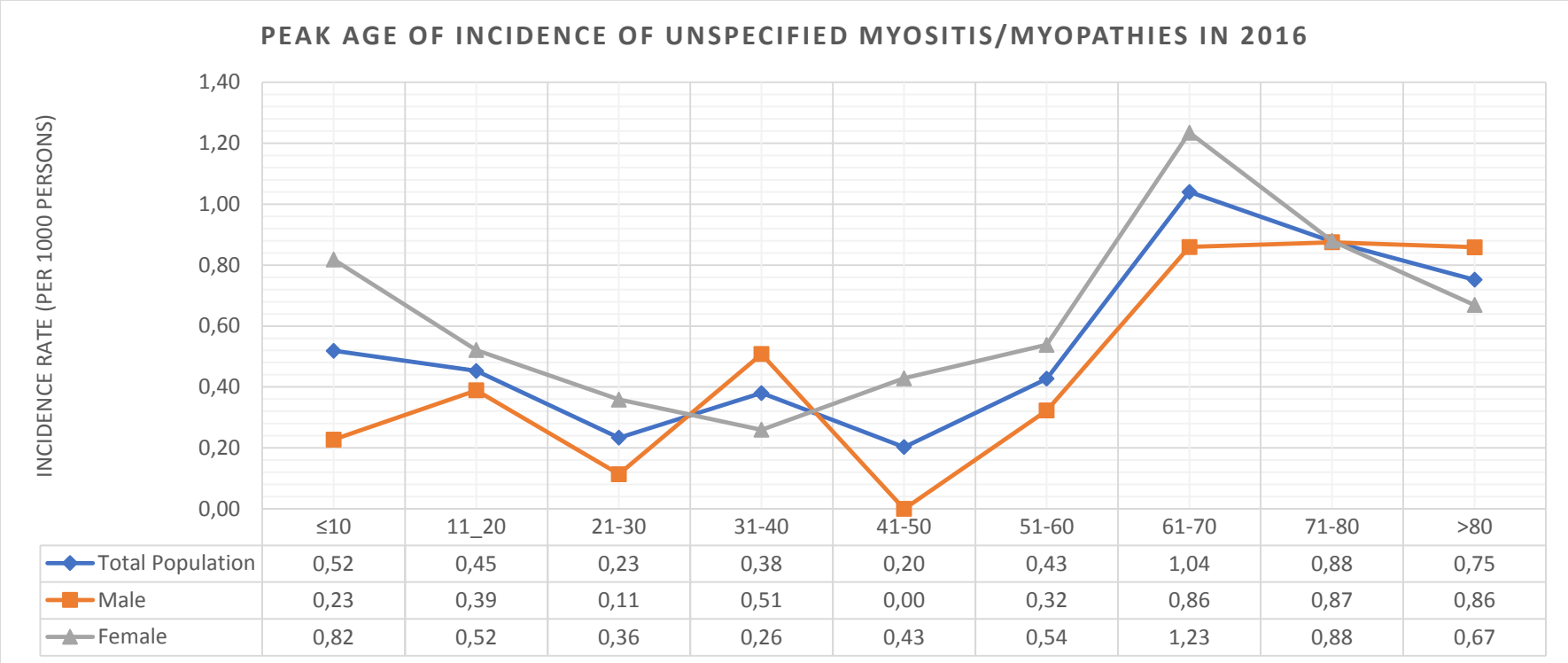


Fig 4.16: Peak Age of Incidence of Unspecified Myositis/Myopathies in 2015

Fig. 4.16 shows that the overall peak age of incidence was 51-60 years in 2015. In 2015, the peak age incidence among men was different 71-80 years. However, the peak age of prevalence among women was similar to the overall incidence graph 51-60 years of age.

4.8c: Peak Age of Incidence of Unspecified Myositis/Myopathies in 2016



	≤10	11_20	21-30	31-40	41-50	51-60	61-70	71-80	>80
Total Population	0,52	0,45	0,23	0,38	0,20	0,43	1,04	0,88	0,75
Male	0,23	0,39	0,11	0,51	0,00	0,32	0,86	0,87	0,86
Female	0,82	0,52	0,36	0,26	0,43	0,54	1,23	0,88	0,67

Fig 4.17: Peak Age of Incidence of Unspecified Myositis/Myopathies in 2016

Fig. 4.17 shows that the overall peak age of incidence was 61-70 years in 2016. In 2016, the peak age incidence among men was different 71-80 years. However, the peak age of prevalence among women was similar to the overall incidence graph 61-70 years of age.

4.8d: Peak Age of Incidence of Unspecified Myositis/Myopathies in 2018

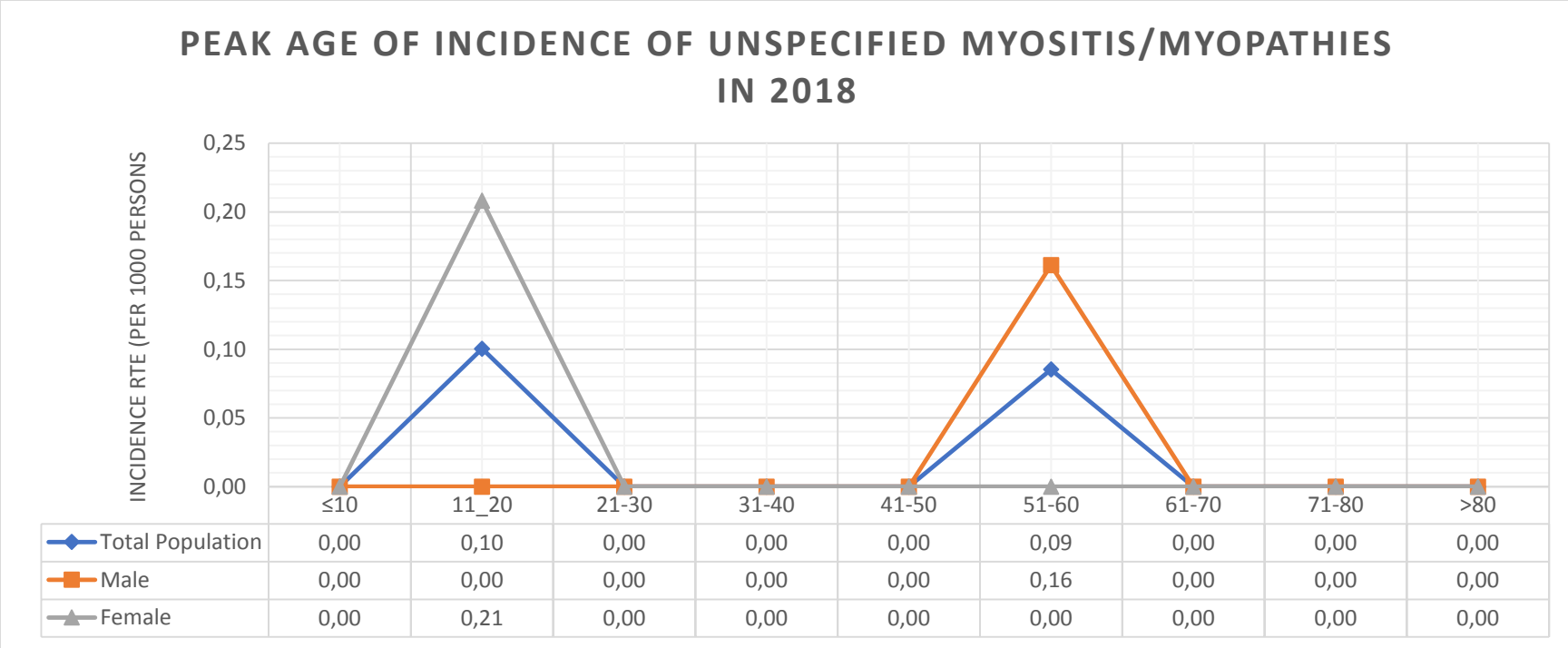


Fig 4.18: Peak Age of Incidence of Unspecified Myositis/Myopathies in 2018

Fig. 4.18 shows that the overall peak age of incidence was 11-20 years in 2018. In 2018, the peak age incidence among men was different 51-60 years. However, the peak age of prevalence among women was similar to the overall incidence graph 11-20 years of age.

4.9 Association between Social demographic characteristics

Table 4.9a: Trend Analysis by Age group and Sex

Variable							df	χ2 (p-value)	*95% Confidence Interval (p-value)*	
Sex	**2014**	**2015**	**2016**	**2017**	**2018**					
	Freq (%)	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Total (%)**			**Lower Limit**	**Upper Limit**
Male	23(50.0)	11(55.0)	19(38.8)	0(0.0)	1(33.3)	54(45.8)				
Female	23(50.0)	9(45.0)	30(61.2)	0(0.0)	2(66.7)	64(54.2)	4	1.394 (0.375)	0.288	0.462
Total	**46(100)**	**20(100)**	**49(100))**	**0(0.0)** 0(0.0)	**3(100)**	**118(100)**				
Age										
≤10	2(4.3)	3(15.0	9(18.4)	0(0.0)	0(0)	14(11.9)	24	3.968 (0.050) *	0.011	0.089
11-20	8(17.4)	1(5.0)	9(18.4)	0(0.0)	2(66.7)	20(16.9)				
21-30	4(8.7)	2(15.0)	4(8.2)	0(0.0)	0(0)	11(9.3)				
31-40	5(10.9)	3(15.0)	6(12.2)	0(0.0)	0(0)	14(11.9)				
41-50	5(10.9)	3(15.0)	3(6.1)	0(0.0)	0(0)	11(9.3)				
51-60	7(15.2)	5(25.0)	5(10.2)	0(0.0)	1(33.3)	18(15.3)				
61-70	6(13.0)	1(5.0)	7(14.3)	0(0.0)	0(0)	14(11.9)				
71-80	4(8.7)	1(5.0)	4(8.2)	0(0.0)	0(0)	9(7.6)				
>80	5(10.9)	0(0)	2(4.1)	0(0.0)	0(0)	7(5.9)				
Total	46(100)	20(100)	49(100)	**0(0.0)**	3(100)	118(100)				

Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval, χ2= chi-square test statistics, df= degree of freedom.

In the table 4.9a, among sex, the females had higher proportions across the years (2014-2018) compared to that of the male we hereby fail to reject the null hypothesis which postulates that, ***there is no significant higher proportion of females to males who have Unspecified Myositis/Myopathies from 2014 -2018 in Saint Vincent and the Grenadines*** due to there was no statistically significant

association observed *(p>0.05).* Among the age group, those within the age group of 20-60 years had significantly higher proportions across the years (2014-2018) compared to that of other age groups, this difference was statistically significant *(p<0.05).*

Table 4.9b: Association between Social demographic characteristics

Variable	Presence of Comorbidity			df	χ2 (p-value)	*95% Confidence Interval (p-value)*	
	Yes Freq (%)	No Freq (%)	Total (%)			Lower Limit	Upper Limit
Sex							
Male	5(71.4)	49(44.1)	**54(45.8)**	**1**	**1.029 (0.310)** [Y]		
Female	2(28.6)	62(55.9)	**64(54.2)**				
Total	**7(100)**	**111(100)**	**118(100)**				
Age							
≤10	1(14.3)	13(11.7)	14(11.9)	8	9.769 (0.067) [F]	0.022	0.111
11-20	0(0.0)	20(18.0)	20(16.9)				
21-30	0(0.0)	11(9.9)	11(9.3)				
31-40	0(0.0)	14(12.6)	14(11.9)				
41-50	0(00	11(9.9)	11(9.3)				
51-60	1(14.3)	17(15.3)	18(15.3)				
61-70	3(42.9)	11(9.9)	14(11.9)				
71-80	2(28.6)	7(6.3)	9(7.6)				
>80	0(0)	7(6.3)	7(5.9)				
Total	**7(100)**	**111(100)**	**118(100)**				

Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval), Y= Yates Correction, χ2= chi-square test statistics, df= degree of freedom

In the table 4.9b, among sex, the males had significant higher proportions to having a comorbidity (diabetes mellitus type 2) compared to that of the female. However, there was no statistically significant association observed *(p>0.05).*

Table 4.9c: Association between Social demographic characteristics

Variable	**Sex**			**df**	**χ2 (p-value)**	***95% Confidence Interval (p-value)***	
Sex	**Male**	**Female**					
	Freq (%)	**Freq (%)**	**Total (%)**			**Lower Limit**	**Upper Limit**
Age							
≤10	3(5.6)	11(17.2)	14(11.9)	8	15.173 (0.075) [F]	0.028	1.222
11-20	8(14.8)	12(18.8)	20(16.9)				
21-30	5(9.3)	6(9.4)	11(9.3)				
31-40	9(16.7)	5(7.8)	14(11.9)				
41-50	3(5.6)	8(12.5)	11(9.3)				
51-60	9(16.7)	9(14.1)	18(15.3)				
61-70	9(16.7)	5(7.8)	14(11.9)				
71-80	7(13.0)	2(3.1)	9(7.6)				
>80	1(1.9)	6(9.4)	7(5.9)				
Total	**54(100)**	**64(100)**	**118(100)**				

Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval), χ2= chi-square test statistics, df= degree of freedom.

In table 4.9c, those within the age group of 36-40 years had higher proportions of both males and females compared to that of other age groups to having diabetics mellitus type 1, however, there was no statistically significant association observed between age and sex *(p>0.05).*

4.10; Socio-demographics Characteristics of Patients with Systemic Lupus Erythematous (SLE)

Table 4.10: Socio-demographics Characteristics of Patients with Systemic Lupus Erythematous (SLE)

Variable	Frequency (n=27)	Percentage (%)
Age		
≤10	1	3.7
11-15	4	14.8
16-20	3	11.1
21-25	4	14.8
26-30	2	7.4
31-35	7	25.9
36-40	1	3.7
41-45	1	3.7
46-50	3	11.1
51-55	0	0.0
56-60	1	3.7
Mean ± S.D (28.52 ± 13.03) yrs. old, 95% C.I for Mean (23.36-33.68), Median Age = 30 yrs. old		
Sex		
Male	2	7.4
Female	25	92.6
Year		
2014	4	14.8
2015	4	14.8
2016	11	40.7
2017	6	22.2
2018	2	7.4

S. D=Standard deviation, C. I= Confidence Interval

Table 4.7, shows the socio-demographic distribution of patients with Systemic Lupus Erythematous (SLE) with respect to age, sex. From 2014 to 2018, the total number of cases of Systemic Lupus Erythematous (SLE) in Milton Cato General Hospital was 27, with more than one-third 11(40.7%) occurring in the year 2016. Among the cases of Systemic Lupus Erythematous (SLE) the mean age was ***28.52 ± 13.03*** and the ***median Age= 30yrs old, almost all 25(92.6%) were females.***

4.11 Incidence of Systemic Lupus Erythematous (SLE) from 2014 -2018

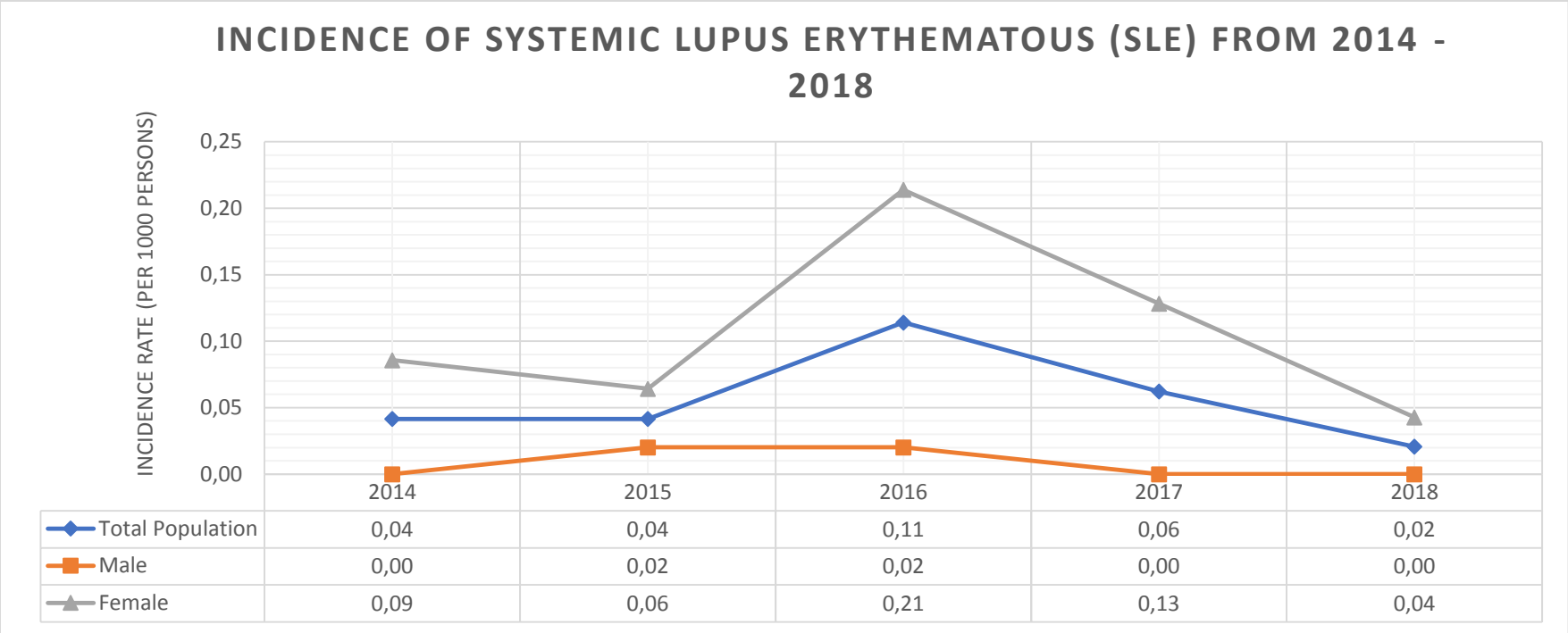
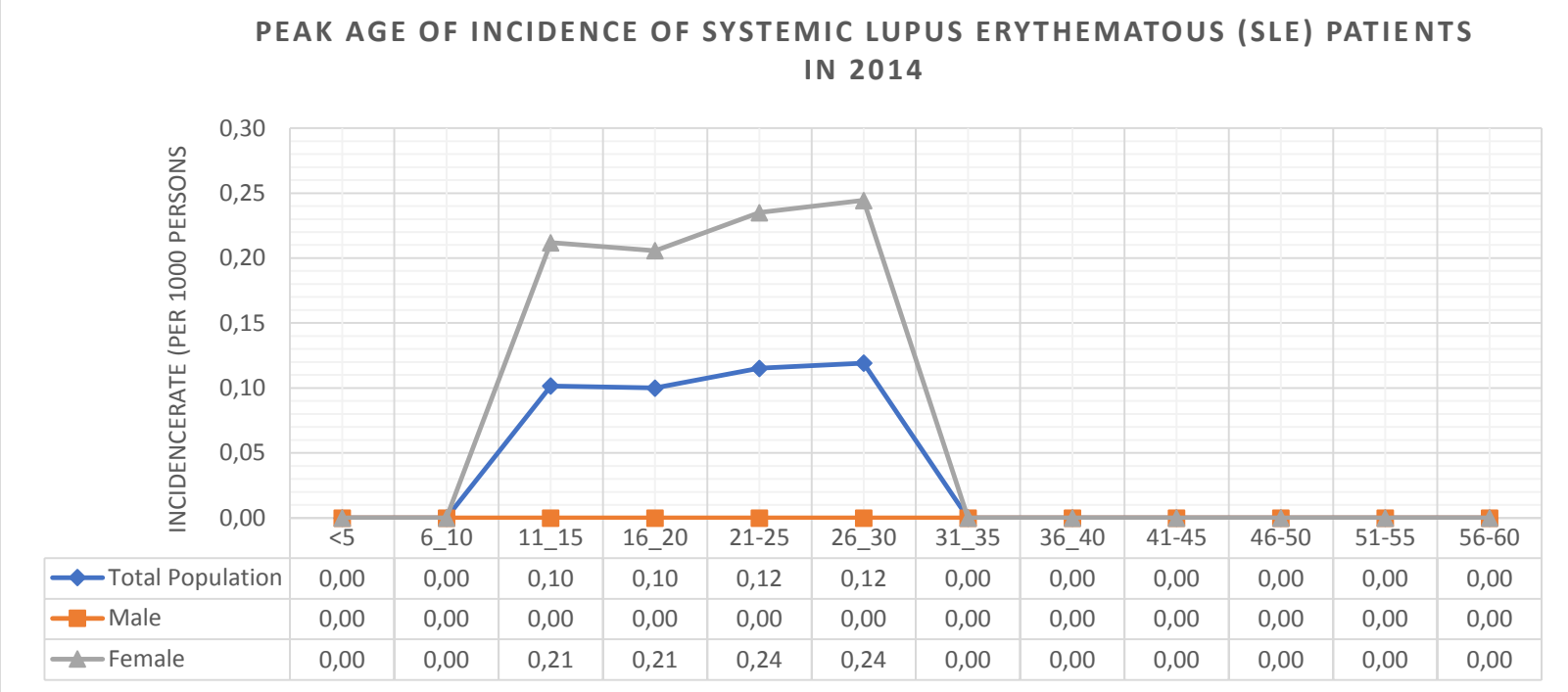


Fig 4.19: Incidence of Systemic Lupus Erythematous (SLE) from 2014 -2018

Fig. 4.19: shows the trend in incidence by year. Every year, women showed a significantly higher incidence of Systemic Lupus Erythematous (SLE), there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2016 (0.11/1000 person-years). The lowest incidence was noted in 2018 (0.02/1000 person-years). Among sex, there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2015 and 2016 for males (0.02/1000 person-years) respectively and in 2016 for females (0.21/1000 person-years). The lowest incidence was noted in 2018 (0.00/1000 person-years) and (0.04./1000 person-years) for both male and female respectively

4.11b: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2014

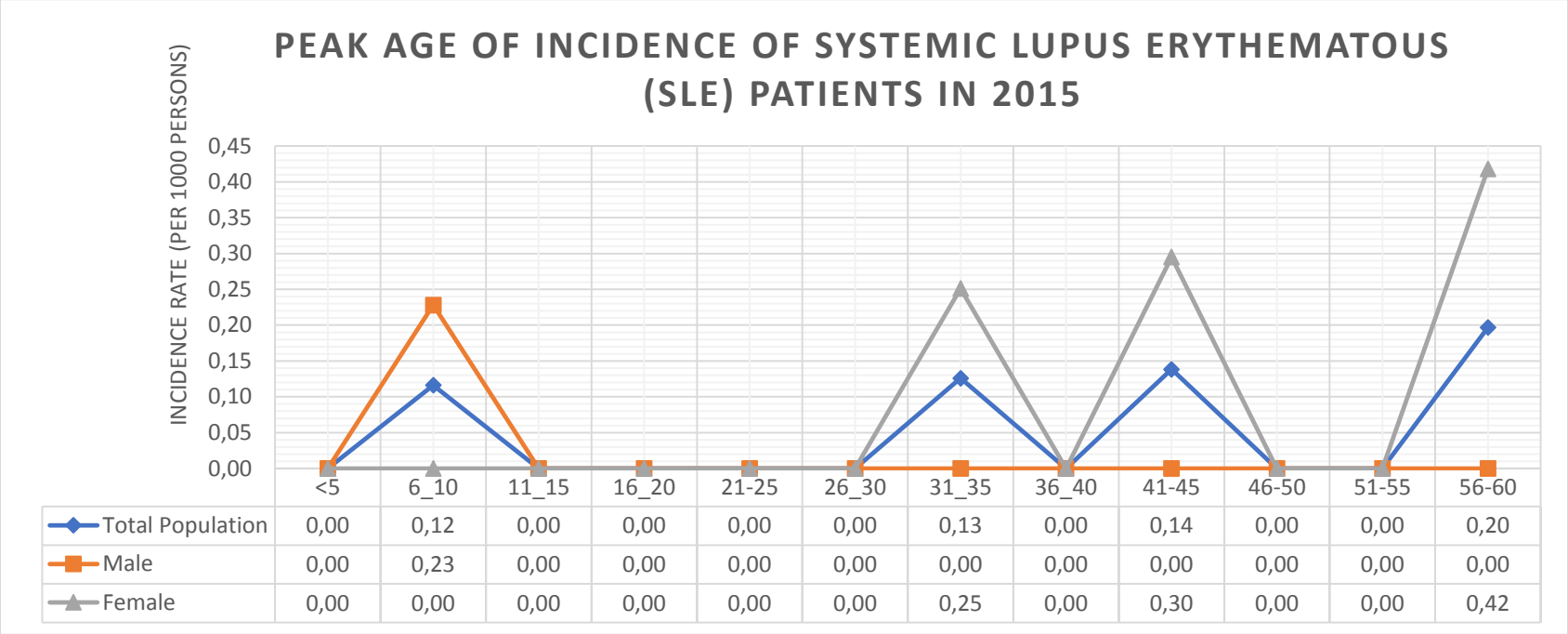


	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60
Total Population	0,00	0,00	0,10	0,10	0,12	0,12	0,00	0,00	0,00	0,00	0,00	0,00
Male	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Female	0,00	0,00	0,21	0,21	0,24	0,24	0,00	0,00	0,00	0,00	0,00	0,00

Fig 4.20: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2014

Fig. 4.20 shows that the overall peak age of incidence was between 21-30 years in 2014. In 2014, there were no cases of SLE among males. However, the peak age of prevalence among women was similar to the overall incidence graph 21-30 years of age.

4.11c: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2015

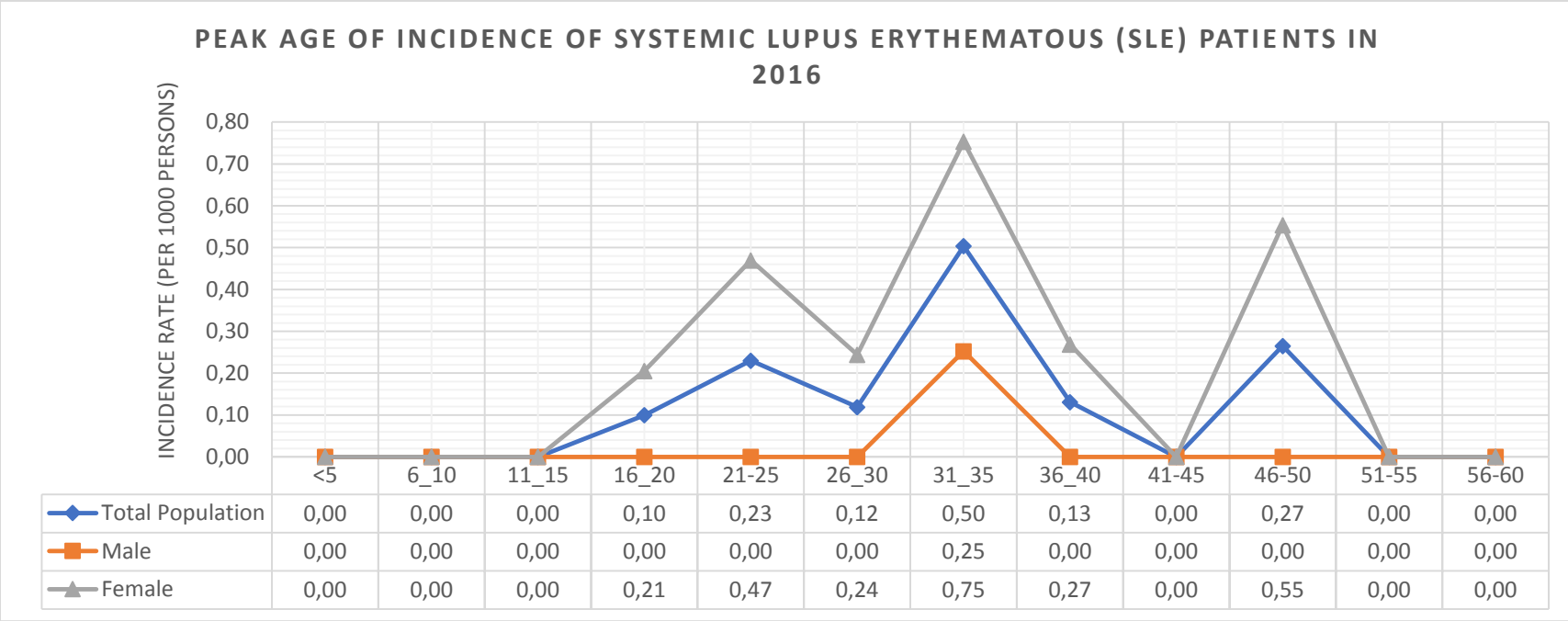


	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60
Total Population	0,00	0,12	0,00	0,00	0,00	0,00	0,13	0,00	0,14	0,00	0,00	0,20
Male	0,00	0,23	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Female	0,00	0,00	0,00	0,00	0,00	0,00	0,25	0,00	0,30	0,00	0,00	0,42

Fig 4.21: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2015

Fig. 4.21 shows that the overall peak age of incidence was between 41-45 years in 2015. In 2015, the peak age incidence among men was different 6-10 years. However, the peak age of prevalence among women was similar to the overall incidence graph 41-45 years of age.

4.11d: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2016

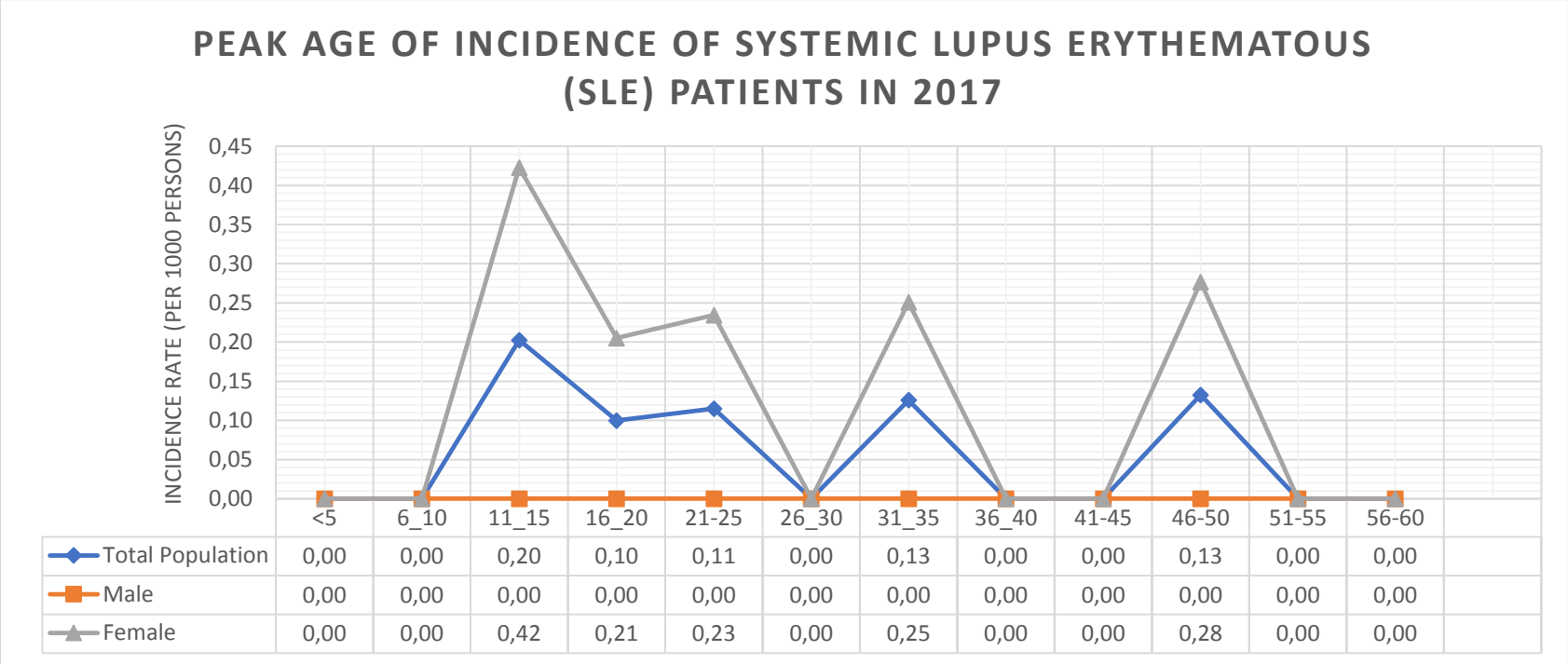


	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60
Total Population	0,00	0,00	0,00	0,10	0,23	0,12	0,50	0,13	0,00	0,27	0,00	0,00
Male	0,00	0,00	0,00	0,00	0,00	0,00	0,25	0,00	0,00	0,00	0,00	0,00
Female	0,00	0,00	0,00	0,21	0,47	0,24	0,75	0,27	0,00	0,55	0,00	0,00

Fig 4.22: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2016

Fig. 4.22 shows that the overall peak age of incidence was between 31-35 years in 2016. In 2016, the peak age incidence among men and women was similar to the overall incidence graph 31-35 years of age.

4.11e: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2017

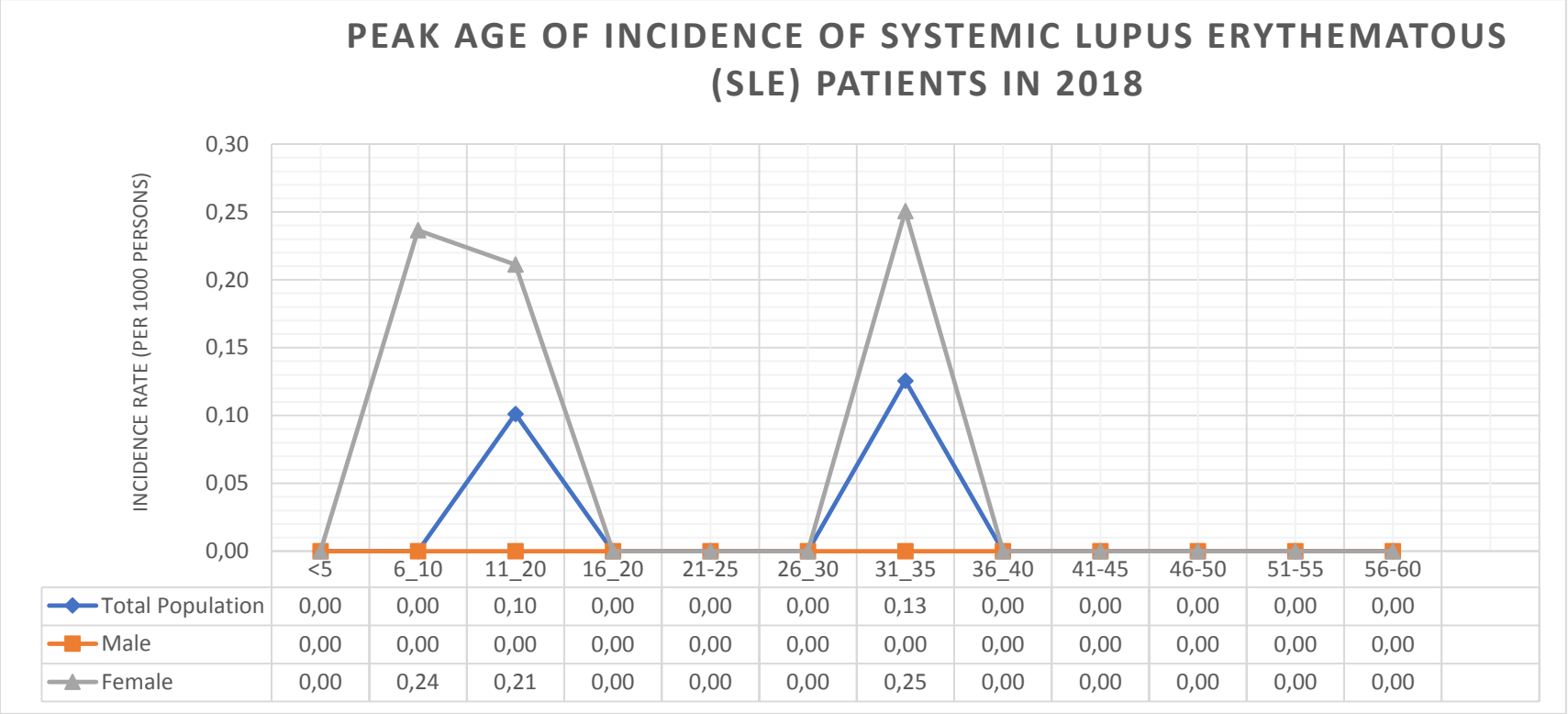


	<5	6_10	11_15	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60
Total Population	0,00	0,00	0,20	0,10	0,11	0,00	0,13	0,00	0,00	0,13	0,00	0,00
Male	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Female	0,00	0,00	0,42	0,21	0,23	0,00	0,25	0,00	0,00	0,28	0,00	0,00

Fig 4.23: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2017

Fig. 4.23 shows that the overall peak age of incidence was between 16-20 years in 2017. In 2017, there was no cases of SLE among males. However, the peak age of prevalence among women was similar to the overall incidence graph 26-20 years of age.

4.11f: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2018



	<5	6_10	11_20	16_20	21-25	26_30	31_35	36_40	41-45	46-50	51-55	56-60
Total Population	0,00	0,00	0,10	0,00	0,00	0,00	0,13	0,00	0,00	0,00	0,00	0,00
Male	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Female	0,00	0,24	0,21	0,00	0,00	0,00	0,25	0,00	0,00	0,00	0,00	0,00

Fig 4.24: Peak Age of Incidence of Systemic Lupus Erythematous (SLE) patients in 2018

Fig. 4.24 shows that the overall peak age of incidence was between 36-40 years in 2018. In 2018, there was no cases of SLE among males. However, the peak age of prevalence among women was similar to the overall incidence graph 36-40 years of age.

4.12 Association between Social demographic characteristics

Table 4.12a: Trend Analysis by Age group and Sex

Variable							df	χ2 (p-value)	*95% Confidence Interval (p-value)*	
Sex	**2014**	**2015**	**2016**	**2017**	**2018**					
	Freq (%)	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Freq (%)**	**Total (%)**			**Lower Limit**	**Upper Limit**
Male	0(0)	1(50.0)	1(9.1)	0(0.0)	0(0.0)	2(7.4)				
Female	4(100)	3(75.0)	10(90.9)	6(100)	2(100)	25(92.6)	4	0.301 (0.767)	0.615	0.918
Total	**4(100)**	**4(100)**	**11(100)**	**6(100)**	**2(100)**	**27(100)**				
Age										
≤10	0(0.0)	1(25.0)	0(0.0)	0(0.0)	0(0.0)	1(3.7)	24	0.013 (0.933)	0.844	1.000
11-15	1(25.0)	0(0.0)	0(0.0)	2(33.3)	1(50.0)	4(14.8)				
16-20	1(25.0)	0(0.0)	1(9.1)	1(16.7)	0(0.0)	3(11.1)				
21-25	1(25.0)	0(0.0)	2(18.2)	1(16.7)	0(0.0)	4(14.8)				
26-30	1(25.0)	0(0.0)	1(9.1)	0(0.0)	0(0.0)	2(7.4)				
31-35	0(0.0)	1(25.0)	4(36.4)	1(16.7)	1(50.0)	7(25.9)				
36-40	0(0.0)	0(0.0)	1(9.1)	0(0.0)	0(0.0)	1(3.7)				
41-45	0(0.0)	1(25.0)	0(0.0)	0(0.0)	0(0.0)	1(3.7)				
46-50	0(0.0)	0(0.0)	2(18.2)	1(16.7)	0(0.0)	3(11.1)				
51-55	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)				
56-60	0(0.0)	1(25.0)	0(0.0)	0(0.0)	0(0.0)	1(3.7)				
Total	**4(100)**	**4(100)**	**11(100)**	**6(100)**	**2(100)**	**27(100)**				

Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval), χ2= chi-square test statistics, df= degree of freedom.

In the table 4.12a, among sex, the females had higher proportions across the years (2014-2018) compared to that of the male we hereby fail to reject the null hypothesis which postulates that, ***there is no significant higher proportion of females to males who have*** Systemic Lupus Erythematous (SLE) ***from 2014 -2018 in Saint Vincent and the Grenadines*** due to there was no statistically significant association observed *(p>0.05).* Among the age group, those within the age group of 31-35 years had significantly higher proportions across the years (2014-2018) compared to that of other age groups, this difference was not statistically significant *(p>0.05).* We hereby fail to reject the null hypothesis which postulates that ***there is no significant higher proportion of individuals ≥ 40 years of age compared to other age groups who have*** Systemic Lupus Erythematous (SLE) ***from 2014 -2018 in Saint Vincent and the Grenadines*.**

Table 4.12b: Association between Social demographic characteristics

Variable	Sex			df	χ2 (p-value)	*95% Confidence Interval (p-value)*	
	Male Freq (%)	Female Freq (%)	Total (%)			Lower Limit	Upper Limit
Age							
≤10	1(50.0)	0(0.0)	1(3.7)	8	11.093 (0.533) [F]	0.355	0.712
11-15	0(0.0)	4(16.0)	4(14.8)				
16-20	0(0.0)	3(12.0)	3(11.1)				
21-25	0(0.0)	4(16.0)	4(14.8)				
26-30	0(0.0)	2(8.0)	2(7.4)				
31-35	1(14.3)	6(24.0)	7(25.9)				
36-40	0(0.0)	1(4.0)	1(3.7)				
41-45	0(0.0)	1(4.0)	1(3.7)				
46-50	0(0.0)	3(12.0)	3(11.3)				
51-55	0(0.0)	0(0.0)	0(0.0)				
56-60	0(0.0)	0(0.0)	1(3.7)				
Total	**2(100)**	**25(100)**	**27(100)**				

Statistically significant (p<0.05). F (Fisher's Exact test) CI = Confidence Interval), Y= Yates Correction, χ2= chi-square test statistics, df= degree of freedom.

In table 4.12b, those within the age group of 31-35 years had higher proportions of both males and females compared to that of other age groups to having Systemic Lupus Erythematous (SLE). However, there was no statistically significant association observed between age and sex *(p>0.05).*

4.13: Case-mortality from Systemic Lupus Erythematous (SLE) from 2014 -2018

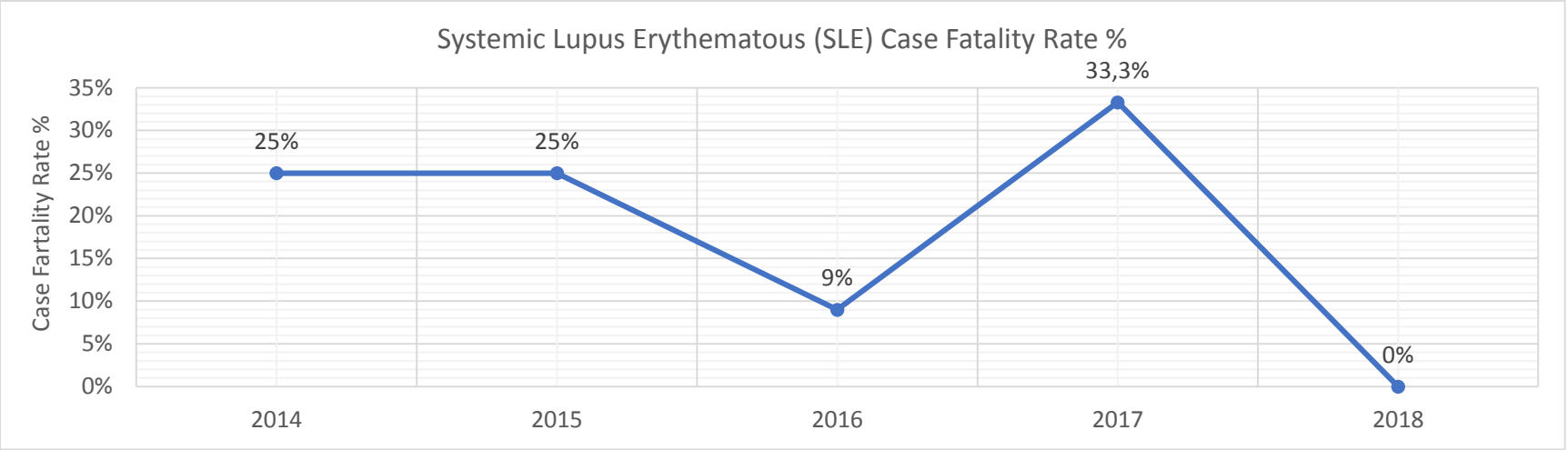


Fig 4.13 shows the case fatality from Diabetics Mellitus Type 1 of the total, 2017 had the highest case fatality of 33% compared to the other years with 2018 having no case fatality at all.

CHAPTER FIVE

DISCUSSION, CONCLUSION, AND RECOMMENDATION

5.0 Introduction

This chapter summarizes the findings of the study. Also, discussion, conclusions, and recommendations from the findings are presented. The purpose of the study was to determine the Temporal trend of the Incidence of Autoimmune Diseases in Saint Vincent and the Grenadines from 2014-2018. The study was guided by 11 objectives.

5.1 Discussion of findings

Findings from the study showed that Type I diabetes was the leading autoimmune disease in the country, which was followed by Myopathies and Myositis. In contrast to the study finding, Aaron *et al*., (2015) in a systematic review reported that celiac disease increased the most and the highest increase in incidence, comparing old to new surveys are allocated to myasthenia gravis. However, the study also indicated that between the countries, celiac disease, type 1 diabetes, and myasthenia gravis frequencies increased the most in Canada, Israel, and Denmark, respectively. In this study I observed a decreasing trend in the incidence of autoimmune diseases, there was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2016 (0.94/1000 person-years). The lowest incidence was noted in 2018 (0.03 - 0.17/1000 person-years). The decrease in trend reported in the present study might be explained due to the use of the hospital database that could stem from the lack of accurate diagnosis which could lead to missed or undiagnosed cases. Another explanation of the findings is that the data analyzed in this study were obtained when subjects visited healthcare institutions. Therefore, no information was available for Autoimmune disease patients who did not visit a healthcare institution, which could underestimate the Autoimmune disease burden. The incidence rate of Autoimmune diseases reported was lower compared to those findings by Aaron *et al*., (2015) in a systematic review who reported a means ± s.d. of the net % increased /year incidence of autoimmune diseases worldwide was 19.1±43.1.

This difference between the incidence rate of both studies can be overestimated or underestimated due to various population sizes of both countries and the difference in multiplier rate (1000 vs 100000) by both studies which impair the basis of comparison. The population size in the Caribbean (Saint Vincent and the Grenadines) was approximately 120,000 people at the time of the study.

Social demographic characteristics of individuals who have Autoimmune disease

The incidence of Autoimmune disease peaked within the age group of 31-40 years, after which it declined slowly. The incidence of Autoimmune disease among females was higher compared to that of males with a peak age occurring at 31-35 years. Findings from the study were in resonate with that of Jacobsen *et al*., (1997) in a systematic review who reported most autoimmune diseases were more common in women and a disproportionate occurrence of these diseases among these women.

Incidence of Type 1 Diabetes Mellitus

In this study I observed a decreasing trend in the incidence of Type 1 Diabetes Mellitus (T1D) with a baseline of 0.49 per1000 person-years 2014 to 0.04 per 1000 person-years in 2018. The decrease in trend reported in the present study might be explained due to the use of the hospital database which could stem from the lack of accurate diagnosis. Another explanation of the findings is that the data analyzed in this study were obtained when subjects visited healthcare institutions. Therefore, no information was available for T1D patients who did not visit a healthcare institution, which could underestimate the T1D burden.

The incidence rate of T1D reported was lower compared to those findings by Karvonen *et al*., (2000) who found an age-adjusted type 1 diabetes incidence difference from 0.1/100,000 per year in China and Venezuela to 36.8/100,000 per year in Sardinia and 36.5/100,000 in Finland. Findings from the study also showed that the lowest incidence (<1/100, 000 per year) was realized from China and South America populations. A similar study carried out by the DIAMOND Project Group (2006), also showed that with an age-adjusted incidence of type 1 diabetes varied from 0.1 per 100,000/year in China and Venezuela to 40.9 per 100,000/year in Finland.

This difference between the incidence rate of both studies can be overestimated or underestimated due to various population sizes of both countries and the difference in multiplier rate (1000 vs 100000) by both studies which impair the basis of comparison. The population size in the Caribbean was approximately 120,000 people as at the time of the study

Social demographic characteristics of individuals who have T1D

The incidence of T1D increased continuously with age until it reached a peak, after which, it declined slowly. The incidence of T1D among females in this study peaks occurring at 31 to 35years. This pattern might be related to a type of diabetes termed late onset Type 1 Diabetes Mellitus which dissimilar with other studies which showed that T1D is the major type of diabetes in youth, accounting for ≥85% of all diabetes cases in youth < 20 years of age worldwide (Vandewalle *et al*., 1997; Thunander *et al*., 2008). In general, the incidence rate increases from birth and peaks between the ages of 10–14 years during puberty (EURODIAB ACE Study Group, 2000) which is in contrast with this study. The increasing incidence of T1D throughout the world is especially marked in young children. Registries in Europe suggest that recent incident rates of T1D were highest in the youngest age-group of 0– 4 years (EURODIAB ACE Study Group 2000). Incidence rates decline after puberty and appear to stabilize in young adulthood (15–29 years). However, a similar study reported that the incidence of T1D in adults is lower than in children, although approximately one-fourth of persons with T1D are diagnosed as adulthood. Clinical presentation occurs at all ages and as late as the 9th decade of life. Up to 10% of adults initially thought to have type 2 diabetes are found to have antibodies associated with T1D and beta-cell destruction in adults appears to occur at a much slower rate than in young T1D cases, often delaying the need for insulin therapy after diagnosis. Individuals diagnosed with autoimmune diabetes when they are adults have been referred to as having latent autoimmune diabetes of adults (Turner *et al*., 1997; Leslie *et al*., 2006; Naik *et al*., 2003).

Also, findings from the study confirmed female predominance in the incidence rate of T1D, with approximately 2-fold higher incidence in women than in men. This finding is similar to some studies who highlighted a distinctive pattern with an observation that regions with a high incidence of T1D (populations of European origin) have a male excess, whereas regions with a low incidence (populations

of non- European origin) report a female excess (Soltesz *et al*., 2007; Green *et al*., 1992; Karvonen *et al*., 1997; Gale *et al*., 2001) which resonates with this study with a baseline of 0.49 per1000 person-years 2014 to 0.04 per 1000 person-years in 2018.

Case-mortality and morbidity from T1D

The study findings found increased mortality in people with T1D compared with the general population with a baseline of 3% in 2014 to 33% in 2018. This implies that one-third of the people that have T1D dies from it. This finding has serious implications on the healthcare of the country, this finding reveals the gap in the management and treatment of TID. This rate was higher than that found by a Norwegian cohort of 1,906 T1D patients diagnosed at <15 years of age between 1973–1982 (46,147 person-years) reported an SMR for all-cause mortality of 4.0 with an SMR of 20 for ischemic heart disease. Acute metabolic complications of T1D were the most common cause of death <30 years of age (Skrivarhaug *et al*., 2006).

However, this difference could be attributed to both rates were unadjusted. The standard mortality ratio (SMR) is more informative than the crude mortality rate because this compares mortality rates to people without SLE of the same age and gender, and therefore assesses the excess mortality due to SLE. Alternatively, it may be due to these cases having a milder disease or the different study methods applied. However, this study didn't compute age-specific mortality rate and sex-specific mortality rate due to a lack of availability of data and poor management health information systems in the country at the time of the study.

Incidence of unspecified myopathy/Myositis

In this study, I observed a decreasing trend in the incidence of Myopathy/Myositis. There was an annual decrease in the incidence from 2014 to 2018, with a peak incidence in 2016 (0.44/1000 person-years). The lowest incidence was noted in 2018 (0.03/1000 person-years). The decrease in trend reported in the present study might be explained due to the use of the hospital database could stem from the lack of accurate diagnosis which could lead to missed or undiagnosed cases. Another explanation of the findings is that the data

analyzed in this study were obtained when subjects visited healthcare institutions. Therefore, no information was available for Myopathy/Myositis patients who did not visit a healthcare institution, which could underestimate the Myopathy/Myositis burden.

The incidence rate of Myopathy/Myositis reported was lower compared to those findings by Alain *et al*., (2014) who found an overall incidence to be estimated at 7.98 cases/million year (95% CI -7.38, 8.66) between 1951 and 2010 from the results of 16 surveys in which incidence ranged from 1.16 to 19 /million/year (95% CI -17, 21). The frequency of IM increased over time, which may reflect progress in diagnostic performance, although there is still a need to increase the level of awareness with regard to these diseases. This difference between the incidence rate of both studies can be overestimated or underestimated due to various population sizes of both countries and the difference in multiplier rate (1000 vs 100000) by both studies which impair the basis of comparison. The population size in the Caribbean (Saint Vincent and the Grenadines) was approximately 120,000 people at the time of the study.

Social demographic characteristics of individuals diagnosed with unspecified myopathy/myositis

The incidence of Myopathy/Myositis peaked within the age group of 11-20 years, after which it declined slowly. The incidence of Myopathy/Myositis among females was higher compared to that of males with a peak age occurring at 11-20 years. Findings from the study were in contrast with that of Jun Ann *et al*., (2011) in which the youngest patient was 35 years of age. However, there were similar findings Jun Ann *et al*., (2011) reported in South Australia which showed that out of the population group comprised 209 females (59%) and 144 males (41%). Both dermatomyositis and polymyositis groups demonstrated a female preponderance with an F:M ratio of 2.75 (33 females, 12 males) and 1.55 (110 females, 71 males), respectively.

Only a few, 7(5%) had comorbidities been diabetes mellitus type 2, with the males having significantly higher proportions compared to that of the female. Findings from the study were dissimilar with that of Soo Kyung Cho *et al*., (2019) in Korea who reported more than two-thirds of patients (70.7%) had more than two comorbidities. Twenty percent of patients had interstitial lung diseases.

Incidence of Systemic Lupus Erythematous (SLE)

In this study I observed a decreasing trend in the incidence of SLE with a baseline of 0.04 per1000 person-years 2014 to 0.02 per 1000 person-years in 2018. The decrease in trend reported in the present study might be explained by the poor diagnostic or confirmatory test to confirm the diagnosis using American College of Rheumatology (ACR) criteria or a renal biopsy of lupus nephritis/end-stage renal disease or a rheumatologist's diagnosis, this gap of poor diagnosis could underestimate or mask the actual burden of SLE. Also due to the use of the hospital database could stem from the lack of accurate diagnosis. Another explanation of the findings is that the data analyzed in this study were obtained when subjects visited healthcare institutions. Therefore, no information was available for SLE patients who did not visit a healthcare institution, which could underestimate the SLE burden.

The incidence rate of SLE reported was lower compared to that reported in Korea who reported an incidence rate of (5.42/100,000 person-years in 2005 to 3.6/100,000 person-years), in the Latin America and Incidence rate of 4.7 to 8.7/per/ 100000 person's years was reported, in North America, an incidence rate of 23.2/100 000 person-years was reported while in Africa and Ukraine an incidence rate of (0.3/100 000 person-years). Eun Hui *et al*., 2020; Scolnik & Soriano 2016; Rees *et al*., 2017 This difference between the incidence rate of both studies can be overestimated or underestimated due to various population size of both countries and the difference in multiplier rate (1000 vs 100000) by both studies which impair the basis of comparison. The population size in the Caribbean was approximately 120,000 people as at the time of the study

Social demographic characteristics of individuals who have (SLE)

The incidence of SLE increased continuously with age until it reached a peak, after which, it declined slowly. The incidence of SLE among females in this study peaks occurring at 31 to 35years. This pattern might be related to the use of contraceptive pills during the reproductive age. The incidence of SLE had a peak in their middle age 31 to 35 years of age, however, this could be attributable to the small numbers of males in the study. This finding was similar to a study from Norway by Lerang *et al.*, 2012. Also, findings from the study confirmed female predominance in the incidence rate of SLE, with approximately 10-fold higher prevalence in women than in

men. Studies have reported that this ratio tends to increase with age and peaks during the childbearing ages, declining slowly thereafter (Lerang et al., 2012; Nightingale et al., 2007). The female-to-male ratio of patients with SLE was similar to that reported previously by Dall'Era *et al*., 2017 & Izmirly *et al*., 2006 who reported a higher incidence rate of SLE in women compared with men and in African Americans compared to Caucasians as most natives in Saint Vincent and the Grenadines are of African descent. Barbhaiya *et al*., 2017 also reported that from Medicaid data from 2000 to 2010 and identified 65788 SLE patients- 93.1% were women. This study finding was similar to that of Ingvarsson *et al*. 2016, Francis *et al*., 2018 & Hermansen *et al*., 2016 who reported sex-specific incidence rates of SLE were higher in women than men.

Case-mortality and morbidity from Systemic Lupus Erythematous (SLE)

The study findings found increased mortality in people with SLE compared with the general population. This study shows a mortality rate of 33%, meaning one-third of the people that have SLE dies from it. This finding has serious implications on the healthcare of the country, this finding reveals the gap in management and treatment. This rate was higher than that found by Costenbader *et al*., 2015 in the US who reported SLE mortality rates per 1000 patient-years among Native American (27.52), Caucasian (20.17), and African American (24.13) patients and were lower among Hispanic (7.12) or Asian (5.18) patients. Also, Francis *et al*., (2016) reported a mortality rate of 15.84/1000 person-years (95% CI-13.91, 18.04)

However, this difference could be attributed to both rates were unadjusted and our cohort was on average older than Costenbader *et al*., 2015 and Francis *et al*., 2016. The SMR is more informative than the crude mortality rate because this compares mortality rates to people without SLE of the same age and gender and therefore assesses the excess mortality due to SLE. Alternatively, it may be due to our cases having a milder disease or to the different study methods used. However, this research didn't compute age-specific mortality rate and sex-specific mortality rate due to a lack of availability of data and/or poor management health information system in the country at the time of the study.

5.2: Conclusion

Sequel to the findings of my research, this study showed that the incidence of autoimmune disease, Type 1 diabetes Mellitus Myopathy/Myositis, and SLE in Saint Vincent have decreased in the last decade, whereas the mortality rates of both SLE and Type 1 Diabetes Mellitus have increased. This finding of increased mortality of SLE and T1D suggests that this disease is no longer rare and will have implications for future healthcare planning. Age and sex were found to be risk factors for SLE. Our data confirmed the known predilection of SLE in women. The peak age of diagnosis is middle age, contrary to the generally held belief that lupus mainly targets young people.

5.3 Recommendations:

Implication for policy

Disease Registries should be expanded to a population-based multidisciplinary autoimmune disease registry to enhance the collection and analysis of data over time on causation, natural history, morbidity, and mortality of autoimmune diseases. Utilizing a multidisciplinary, integrated approach with collection of data on multiple diseases. Support research on the feasibility and optimal design of the registry to allow the collation of data at all levels. Provide epidemiology, statistical, clinical disease, and bioinformatics expertise, incorporate biomarker data in registries, and provide infrastructure for long-term support of registries and epidemiology studies.

Provide long-term support for existing genetic repositories; establish genetic repositories for additional autoimmune disorders; ensure adequate representation of disease phenotypes and races. Develop highly standardized, specific, and sensitive laboratory assays for infectious and non-infectious environmental factors that can be used in large epidemiologic studies.

From key findings from Type1 Diabetes mellitus, reinforcing the need for improved access to insulin, glucometers, and test strips in low-income countries like ours. Three tiers of care (minimal, intermediate and comprehensive) have been defined by the availability of

insulin and blood glucose monitoring regimens, requirements for HbA1c testing, complications screening, diabetes education, and multidisciplinary care, and it is expected that policy-makers will aspire to attain the highest levels of care possible given the resources available.

Implication for practice

Identify new opportunities and continue support for training and career development for new and established basic science and clinical investigators in autoimmune disease research, including specialized training in epidemiology and bioinformatics. Provide increased training opportunities for health care professionals by establishing collaborative training programs between professional and non-profit health organizations and clinical programs for research in autoimmune disease. The training and re-training of healthcare workers at all levels to promptly recognize and treat these conditions and their co-morbidities in timely manners can be not overemphasized.

Develop and promote the use of a wide range of educational programs and continuing medical education materials in autoimmune disease for health care professionals, incorporating the latest research advances on autoimmunity and autoimmune diseases. Develop communication and information dissemination strategies for health care providers, patients and their families, and the public using a broad range of formats and technologies to maximize access that incorporates current information resources. Develop a public awareness campaign for autoimmune diseases in collaboration with private organizations and public service agencies.

Develop culturally sensitive public awareness information materials aimed at patients, families, and health care providers of diverse races and ethnicities. Establish a centralized, consolidated autoimmunity/autoimmune disease information center accessible to professionals and the public via the Internet, where there is a provision of information about clinical trials to evaluate prevention and treatment regimens that will enable patients and their physicians to make informed decisions.

Implication for research

The present literature survey is not aiming to investigate etiologies or environmental factors affecting autoimmune induction or progression. It is expected that improved knowledge of the worldwide distribution of autoimmune disorders will help to understand the role of different genetic factors and different environmental influences involved in auto-immunogenesis. At a public level, epidemiological studies are necessary to assess the social and economic burdens impacting the health systems in the country.

The is a need to support researches and trials in stem cell treatment, and provide resources for production, storage, and distribution of materials and probes for genetic research to the research community centrally, that may be usefully in the nearest future in providing an absolute cure for immunological diseases through regenerative medicine.

Support research to develop novel assays to identify prior exposures to environmental agents, including chemicals, toxins, and infectious agents. Support basic and clinical research on mechanisms by which infectious agents or other environmental factors may trigger or modulate autoimmunity or autoimmune diseases. Facilities and medical institutions should be upgraded and supported with government policies with functional collaborations for production and distribution of specialized reagents for research, like MHC-tetramers, antibodies, and microarrays, and advanced researches on mechanisms/pathogenesis, loss of self-tolerance, mechanisms to control autoreactive cells(stem cells therapy), tissue specificity, target organ recognition in different autoimmune diseases.

Expand support for bioengineering, bioimaging research and development and procurement of large instruments and shared facilities. Support development of imaging instrumentation to assess immune function i*n vivo.* Accelerate the development of high-resolution instruments for evaluation of structural damage in autoimmune diseases, e.g., joints, kidneys, brain.

Support basic research leading to the development of probes to assess end-organ function, e.g., technologies for the measurement of the pancreatic islet and beta-cell mass. Support preclinical and clinical research on cell and tissue engineering, organ repair and regeneration, and advanced prosthetic devices. Promote collaborations among engineers, chemists, physicists, and the immunology research community through workshops, symposia, and research solicitations.

Thus, it is imperative to focus on expansive clinical trials which compare the appropriateness of diverse diabetes medications to provide the guidelines for healthcare providers on which patients to prescribe certain drugs. There tends to be a decrease in diabetes complications in certain parts of the world, and the survival and quality of life have improved tremendously, but financial constraints and awareness have restricted ample access to type 1 diabetes prevention, control, and treatment, as well as meeting the informed inventiveness and creativity of gadgets, such as the closed-loop systems. The essential management and access to medicinal drugs are more imperative than high-tech systems in developing countries or elsewhere. There is extant optimism with opportunities for the future in unraveling the metabolic and cellular processes in convergence for researchers, clinicians, healthcare providers, and policymakers to undertake intensive measures regarding the issues, challenges, and presenting opportunities underlying type 1 diabetes and its sequelae which are solvable.

Lastly, stem cell therapy is showing lots of promises in the management of most immunological diseases. We can tap into the future by encouraging researchers and clinicians in trials of stem cell therapy trials for these diseases to achieve optimum care/cure for our daily increasing number of patients in the Caribbean (Saints Vincent and the Grenadines in view).

References

TAN, J. A., ROBERTS-THOMSON, P. J., BLUMBERGS, P., HAKENDORF, P., COX, S. R., & LIMAYE, V. (2013). Incidence and prevalence of idiopathic inflammatory myopathies in South Australia: a 30-year epidemiologic study of histology-proven cases. *International Journal of Rheumatic Diseases*, *16*(3), 331–338. https://doi.org/10.1111/j.1756-185x.2011.01669.x

Meyer, A., Meyer, N., Schaeffer, M., Gottenberg, J. E., Geny, B., & Sibilia, J. (2014). Incidence and prevalence of inflammatory myopathies: A systematic review. *Rheumatology (United Kingdom)*, *54*(1), 50–63. https://doi.org/10.1093/rheumatology/keu289

Cho, S. K., Kim, H., Myung, J., Nam, E., Jung, S. Y., Jang, E. J., … Sung, Y. K. (2019). Incidence and prevalence of idiopathic inflammatory myopathies in Korea: A nationwide population-based study. *Journal of Korean Medical Science*, *34*(8), 1–11. https://doi.org/10.3346/jkms.2019.34.e55

Walsh, S. J., & Rau, L. M. (2000). Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. *American journal of public health*, *90*(9), 1463–1466. https://doi.org/10.2105/ajph.90.9.1463

Jacobson, D. L., Gange, S. J., Rose, N. R., & Graham, N. M. (1997). Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clinical immunology and immunopathology*, *84*(3), 223–243. https://doi.org/10.1006/clin.1997.4412

Lerner, A., Jeremias, P., & Matthias, T. (2015). The world incidence and prevalence of autoimmune diseases is increasing. *International Journal of Celiac Disease*, *3*(4), 151–155. https://doi.org/10.12691/ijcd-3-4-8

Cho, S. K., Kim, H., Myung, J., Nam, E., Jung, S. Y., Jang, E. J., … Sung, Y. K. (2019). Incidence and prevalence of idiopathic inflammatory myopathies in Korea: A nationwide population-based study. *Journal of Korean Medical Science*, *34*(8), 1–11. https://doi.org/10.3346/jkms.2019.34.e55

Meyer, A., Meyer, N., Schaeffer, M., Gottenberg, J. E., Geny, B., & Sibilia, J. (2014). Incidence and prevalence of inflammatory myopathies: A systematic review. *Rheumatology (United Kingdom)*, *54*(1), 50–63. https://doi.org/10.1093/rheumatology/keu289

Ferucci, E., Johnston, J., Gaddy, J., Sumner, L., Posever, J., & Choromanski, T. et al. (2014). Prevalence and Incidence of Systemic Lupus Erythematosus in a Population-Based Registry of American Indian and Alaska Native People, 2007-2009. *Arthritis & Rheumatology*, *66*(9), 2494-2502. doi: 10.1002/art.38720

Dall'Era, M., Cisternas, M., Snipes, K., Herrinton, L., Gordon, C., & Helmick, C. (2017). The Incidence and Prevalence of Systemic Lupus Erythematosus in San Francisco County, California: The California Lupus Surveillance Project. *Arthritis & Rheumatology*, *69*(10), 1996-2005. doi: 10.1002/art.40191

Izmirly, P., Wan, I., Sahl, S., Buyon, J., Belmont, H., & Salmon, J. et al. (2017). The Incidence and Prevalence of Systemic Lupus Erythematosus in New York County (Manhattan), New York: The Manhattan Lupus Surveillance Program. *Arthritis & Rheumatology*, *69*(10), 2006-2017. doi: 10.1002/art.40192

Otsa, K., Talli, S., Harding, P., Parsik, E., Esko, M., Teepere, A., & Tammaru, M. (2017). Prevalence and incidence of systemic lupus erythematosus in the adult population of Estonia. *Lupus*, *26*(10), 1115-1120. doi: 10.1177/0961203316686705

Ingvarsson, R., Bengtsson, A., & Jönsen, A. (2016). Variations in the epidemiology of systemic lupus erythematosus in southern Sweden. *Lupus*, *25*(7), 772-780. doi: 10.1177/0961203316635288

Yen E, Shaheen M, Woo JM, Mercer N, Duan L, Li N, Karlamangla A, McCurdy DK, Singh RR (2016). Temporal Trends in SLE Mortality According to Sex, Race, Ethnicity, and Geographic Region in the United States over the Past Five Decades [abstract]. Arthritis Rheumatol.; 68 (suppl 10) https://acrabstracts.org/abstract/temporal-trends-in-sle-mortality-according-to-sex-raceethnicity-and-geographic-region-in-the-united-states-over-the-past-ve-decades/. Accessed May 29, 2020.

Rees, F., Doherty, M., Grainge, M., Lanyon, P., Davenport, G., & Zhang, W. (2016). Mortality in systemic lupus erythematosus in the United Kingdom 1999–2012. *Rheumatology*, *55*(5), 854-860. doi: 10.1093/rheumatology/kev424

Rees, F., Doherty, M., Grainge, M., Lanyon, P., & Zhang, W. (2017). The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology*, *56*(11), 1945-1961. doi: 10.1093/rheumatology/kex260

M, S., & ER, S. (2016). Epidemiology of Lupus in Latin America. *Lupus: Open Access*, *01*(02). doi: 10.35248/2684-1630.16.1.110

Fatoye, F., Gebrye, T., & Svenson, L. (2018). Real-world incidence and prevalence of systemic lupus erythematosus in Alberta, Canada. *Rheumatology International*, *38*(9), 1721-1726. doi: 10.1007/s00296-018-4091-4

Hermansen, M., Lindhardsen, J., Torp-Pedersen, C., Faurschou, M., & Jacobsen, S. (2017). The risk of cardiovascular morbidity and cardiovascular mortality in systemic lupus erythematosus and lupus nephritis: a Danish nationwide population-based cohort study. *Rheumatology*, kew475. doi: 10.1093/rheumatology/kew475

Arkema, E., Svenungsson, E., Von Euler, M., Sjöwall, C., & Simard, J. (2017). Stroke in systemic lupus erythematosus: a Swedish population-based cohort study. *Annals of The Rheumatic Diseases*, *76*(9), 1544-1549. doi: 10.1136/annrheumdis-2016-210973

Barbhaiya, M., Feldman, C., Guan, H., Gómez-Puerta, J., Fischer, M., & Solomon, D. et al. (2017). Race/Ethnicity and Cardiovascular Events Among Patients with Systemic Lupus Erythematosus. *Arthritis & Rheumatology*, *69*(9), 1823-1831. doi: 10.1002/art.40174

Gómez-Puerta, J., Barbhaiya, M., Guan, H., Feldman, C., Alarcón, G., & Costenbader, K. (2015). Racial/Ethnic Variation in All-Cause Mortality Among United States Medicaid Recipients with Systemic Lupus Erythematosus: A Hispanic and Asian Paradox. *Arthritis & Rheumatology*, *67*(3), 752-760. doi: 10.1002/art.38981

Lee, Y., Choi, S., Ji, J., & Song, G. (2016). Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. *Lupus*, *25*(7), 727-734. doi: 10.1177/0961203315627202

Bae, E., Lim, S., Han, K., Jung, J., Choi, H., & Kim, H. et al. (2020). Trend of prevalence and incidence of systemic lupus erythematosus in South Korea, 2005 to 2015: a nationwide population-based study. *The Korean Journal of Internal Medicine*, *35*(3), 652-661. doi: 10.3904/kjim.2018.303

Cooper, G. S., & Stroehla, B. C. (2003). The epidemiology of autoimmune diseases. *Autoimmunity reviews*, *2*(3), 119–125. https://doi.org/10.1016/s1568-9972(03)00006-5

Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R and et a (2009). Incidence of childhood Type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group; Diabetes. Care 23: 1516-1526.

The DIAMOND Project Group (2006). Incidence and trends of childhood type 1 diabetes worldwide 1990-1999; Diabet Med 23: 857-866.

EURODIAB ACE Study Group (200). Variation and trends in incidence of childhood diabetes in Europe. Lancet 355: 873-876.

Green A and Patterson CC. EURODIAB TIGER Study Group, Europe and Diabetes (2001). Trends in the incidence of childhood-onset diabetes in Europe 1989-1998; Diabetologia 44: 3-8.

Mayer-Davis EJ, Bell RA, Dabelea D, et al (2009). The many faces of diabetes in American youth: type 1 and type 2 diabetes in five race and ethnic populations: the SEARCH for Diabetes in Youth Study. Diab care ;32 (Suppl 2): S99–101

Bell RA, Mayer-Davis EJ, Beyer JW, et al (2009). Diabetes in non-Hispanic white youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diab care ;32 (Suppl 2): S102–S111.

Mayer-Davis EJ, Beyer J, Bell RA, et al (2009). Diabetes in African American youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diab care ;32 (Suppl 2): S112–S122.

Lawrence JM, Mayer-Davis EJ, Reynolds K, et al (2009). Diabetes in Hispanic American youth: prevalence, incidence, demographics, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diab care ;32 (Suppl 2): S123–S132.

Liu LL, Yi JP, Beyer J, et al (2009). Type 1 and Type 2 diabetes in Asian and Pacific Islander U.S. youth: the SEARCH for Diabetes in Youth Study. Diab care ;32 (Suppl 2): S133–S140.

Dabelea D, DeGroat J, Sorrelman C, et al. Diabetes in Navajo youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diab care 2009;32 (Suppl2):S141–S147

Soltesz G, Patterson CC, Dahlquist G (2007). Worldwide childhood type 1 diabetes incidence--what can we learn from epidemiology? Pediatr Diabetes ;8 (Suppl 6):6–14. [PubMed: 17727380]

Green A, Gale EAM, Patterson CC (1992). Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. Lancet: 339:905–909. [PubMed: 1348306]

Karvonen M, Pitkaniemi M, Pitkaniemi J, Kohtamaki K, Tajima N, Tuomilehto J (1997). Sex difference in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data. World Health Organization DIAMOND Project Group. Diabetes Metab Rev: 13:275– 291. [PubMed: 9509279]

Gale EA, Gillespie KM (2001). Diabetes and gender. Diabetol: 44:3–15.

Redondo MJ, Fain PR, Eisenbarth GS (2001). Genetics of type 1A diabetes. Recent Prog Horm Res: 56:69–89. [PubMed: 11237226]

Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T (2008). Concordance for islet autoimmunity among monozygotic twins. N Engl J Med: 359:2849–2850. [PubMed: 19109586]

Redondo MJ, Yu L, Hawa M, et al (2001). Heterogeneity of type I diabetes: analysis of monozygotic twins in Great Britain and the United States. Diabetol: 44:354–362.

Fourlanos S, Dotta F, Greenbaum CJ, et al (2005). Latent autoimmune diabetes in adults (LADA) shouldbe less latent. Diabetol: 48:2206–2212.

Gillespie KM, Gale EA, Bingley PJ (2006). High familial risk and genetic susceptibility in early onset childhood diabetes. Diab: 51:210–214.

Hamalainen AM, Knip M (2002). Autoimmunity and familial risk of type 1 diabetes. Curr Diab Rep: 2:347–353. [PubMed: 12643195]

Barker JM (2006). Type 1 diabetes associated autoimmunity: Natural History, Genetic Associations and Screening. J Clin Endocrinol Metab.

Tsirogianni A, Pipi E, Soufleros K (2009). Specificity of islet cell autoantibodies and coexistence with other organ specific autoantibodies in type 1 diabetes mellitus. Autoimmun Rev: 8:687–691. [PubMed: 19217947]

Mehers KL, Gillespie KM (2008). The genetic basis for type 1 diabetes. Br Med Bull: 88:115–129. [PubMed: 19088009]

Virtanen SM, Knip M (2003). Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age. Am J Clin Nutr: 78:1053–1067. [PubMed: 14668264]

Concannon P, Erlich HA, Julier C, et al (2005). Type 1 diabetes: evidence for susceptibility loci from four genome-wide linkage scans in 1,435 multiplex families. Diab: 54:2995–3001.

Vehik K, Hamman RF, Lezotte D, et al (2008). Trends in high-risk HLA susceptibility genes among Colorado youth with type 1 diabetes. Diab care: 31:1392–1396.

Hermann R, Knip M, Veijola R, et al (2003). Temporal changes in the frequencies of HLA genotypes in patients with Type 1 diabetes-indication of an increased environmental pressure? Diabetol: 46:420–425.

Vandewalle CL, Coeckelberghs MI, De Leeuw IH, et al (1997). Epidemiology, clinical aspects, and biology of IDDM patients under age 40 years. Comparison of data from Antwerp with complete ascertainment with data from Belgium with 40% ascertainment. The Belgian Diabetes Registry. Diab care: 20:1556–1561.

Thunander M, Petersson C, Jonzon K, et al (2008). Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. Diabetes Res Clin Pract: 82:247–255. [PubMed: 18804305]

EURODIAB ACE Study Group (2000). Variation and trends in incidence of childhood diabetes in Europe. Lancet: 355:873–876. [PubMed: 10752702]

Turner R, Stratton I, Horton V, et al (1997). UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. Lancet: 350:1288–1293. [PubMed: 9357409]

Leslie RD, Williams R, Pozzilli P (2006). Clinical review: Type 1 diabetes and latent autoimmune diabetes in adults: one end of the rainbow. J Clin Endocrinol Metab: 91:1654–1659.[PubMed: 16478821]

Naik RG, Palmer JP. Latent autoimmune diabetes in adults (LADA) (2003). Rev Endocr Metab Disord: 4:233–241. [PubMed: 14501174]

Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G (2006). Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetol; 49:298–305.

Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM (2006). All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992–1999. diabetol; 49:660– 666.

Patterson CC, Dahlquist G, Harjutsalo V, et al (2007). Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetol: 50:2439–2442.

Lerang K, Gilboe I, Garen T, Thelle DS, Gran JT (2012). High incidence and prevalence of systemic lupus erythematosus in Norway. Lupus: 21:1362_9.

Nightingale AL, Farmer RD, de Vries CS (2007). Systemic lupus erythematosus prevalence in the UK: methodological issues when using the General Practice Research Database to estimate frequency of chronic relapsing-remitting disease. Pharmacoepidemiol Drug Saf: 16:144-151.

Chukwuma Sr C (2018). Type 1 diabetes mellitus: Issues, challenges and opportunities; Edelweiss Appli Sci Tech 2: 290-297

Drake LA, Dinehart SM, Farmer ER, et al. Guidelines of care for dermatomyositis. American Academy of Dermatology. J Am Acad Dermatol. 1996; 34:824-829.

Dalakas MC. Polymyositis, dermatomyositis and inclusion-body myositis. N Engl J Med. 1991; 325:1487-1498.

Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975; 292:344-347.

Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975; 292:403-407.

Dourmishev AL, Dourmishev LA. Dermatomyositis and drugs. Adv Exp Med Biol. 1999; 455:187-191.

Gerami P, Schope JM, McDonald L, et al. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis siné myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. J Am Acad Dermatol. 2006; 54:597-613.

JP, Wortmann RL. Dermatomyositis. Clin Dermatol. 2006; 24:363-373.
Lundberg IE. The heart in dermatomyositis and polymyositis. Rheumatology (Oxford). 2006;45(suppl 4): iv18-iv21.

Bohan A, Peter JB, Bowman RL, Pearson CM. Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. Medicine (Baltimore). 1977; 56:255-286.
Coyle KM, Plotz PH, Gourley MF. Why isn't my myositis patient getting better? The Rheumatologist. 2008; 2:18, 19, 22.

Alexanderson H, Lundberg IE. The role of exercise in the rehabilitation of idiopathic inflammatory myopathies. Curr Opin Rheumatol. 2005; 17:164-171.

Oddis CV. Idiopathic inflammatory myopathy: management and prognosis. Rheum Dis Clin North Am. 2002; 28:979-1001.

Quain RD, Werth VP. Management of cutaneous dermatomyositis. Am J Clin Dermatol. 2006; 7:341-351.

Sultan SM, Ioannou Y, Moss K, Isenberg DA. Outcome in patients with idiopathic inflammatory myositis: morbidity and mortality. Rheumatology (Oxford). 2002; 41:22-26.

Philip N, Velderman, Leslie A. Bruch, George V. Lawry. Identifying and Managing Dermatomyositis: A Case Report and Review. Rheumatology network.2008; Volume 25

Tersiguel AC, Longueville C, Beltan E, Vincent T, Tressières B, Cordel N. [Prevalence of cancer in the Afro-Caribbean population presenting dermatomyositis and anti-synthetase syndrome: a preliminary study conducted at Pointe-à-Pitre University Hospital, 2000-2012]. Ann Dermatol Venereol. 2014 Oct;141(10):575-80. doi: 10.1016/j.annder.2014.04.112. Epub 2014 May 17. PubMed PMID: 25288059.

Ramos-E-Silva M, Pinto AP, Pirmez R, Cuzzi T, Carneiro SC. Dermatomyositis--Part 1: Definition, Epidemiology, Etiology and Pathogenesis, and Clinics. Skinmed. 2016;14(4):273-279. eCollection 2016. Review. PubMed PMID: 27784516.

Jimenez SA, Derk CT (2004). "Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis". Ann. Intern. Med. 140 (1): 37–50. doi:10.7326/0003-4819-140-2-200401200-00013. PMID 14706971.

Bianchi DW (2000). "Fetomaternal cell trafficking: a new cause of disease?". Am. J. Med. Genet. 91 (1): 22–8. CiteSeerX 10.1.1.605.5548. doi:10.1002/(SICI)1096-8628(20000306)91:1<22::AID-AJMG4>3.0.CO;2-3. PMID 10751084.

Ferri C, Zakrzewska K, Longombardo G, Giuggioli D, Storino FA, Pasero G, Azzi A (1999). "Parvovirus B19 infection of bone marrow in systemic sclerosis patients". Clin. Exp. Rheumatol. 17 (6): 718–20. PMID 10609071.

Sharma SK, Handa R, Sood R, et al. (2004). "Bleomycin-induced scleroderma". The Journal of the Association of Physicians of India. 52: 76–7. PMID 15633728.

Farrant PB, Mortimer PS, Gore M (2004). "Scleroderma and the taxanes. Is there really a link?". Clin. Exp. Dermatol. 29 (4): 360–2. doi:10.1111/j.1365-2230.2004.01519.x. PMID 15245529.

Kettaneh A, Al Moufti O, Tiev KP, et al. (2007). "Occupational exposure to solvents and gender-related risk of systemic sclerosis: a metaanalysis of case-control studies". J. Rheumatol. 34 (1): 97–103. PMID 17117485.

Fonseca C, Lindahl GE, Ponticos M, et al. (September 2007). "A polymorphism in the CTGF promoter region associated with systemic sclerosis". N. Engl. J. Med. 357 (12): 1210–20. doi:10.1056/NEJMoa067655. PMID 17881752.

van Laar JM, McSweeney PA. High-dose immunosuppressive therapy and autologous progenitor cell transplantation for systemic sclerosis. Best Pract Res Clin Haematol 2004; 17: 233-245.

Farge D, Passweg J, van Laar JM, Marjanovic Z, Besenthal C, Finke J, et al. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. Ann Rheum Dis 2004; 63: 974-981.

Tsukamoto H, Nagafuji K, Horiuchi T, Miyamoto T, Aoki K, Takase K, et al. A phase I-II trial of autologous peripheral blood stem cell transplantation in the treatment of refractory autoimmune disease. Ann Rheum Dis 2006; 65: 508-514.

Hough RE, Snowden JA, Wulffraat NM. Haemopoietic stem cell transplantation in autoimmune diseases: a European perspective. Br J Haematol 2005; 128: 432-459.

Urban C, Lackner H, Sovinz P, Benesch M, Schwinger W, Dornbusch HJ, et al. Successful unrelated cord blood transplantation in a 7-year-old boy with Evans syndrome refractory to immunosuppression and double autologous stem cell transplantation. Eur J Haematol 2006; 76: 526-530.

Hunh RD, Fogarty PF, Nakamura R, Read EJ, Leitman SF, Rick ME. High-dose cyclophosphamide with autologous lymphocyte-depleted peripheral blood stem cell (PBSC) support for treatment of refractory chronic autoimmune thrombocytopenia. Blood 2003; 101: 71-77.

Lim SH, Kell J, al-Sabah A, Bashi W, Bailey-Wood R. Peripheral1597.Braz J Med Biol Res 40(12) 2007.Use of stem cells in autoimmune diseases www.bjournal.com.br.blood stem-cell transplantation for refractory autoimmune thrombocytopenic purpura. Lancet 1997; 349: 475.

Seeliger S, Baumann M, Mohr M, Jurgens H, Frosch M, Vormoor J. Autologous peripheral blood stem cell transplantation and anti-Bcell directed immunotherapy for refractory auto-immune haemolytic anaemia. Eur J Pediatr 2001; 160: 492-496.

Bonafede R, Mariotti R. ALS Pathogenesis and Therapeutic Approaches: The Role of Mesenchymal Stem Cells and Extracellular Vesicles. Front Cell Neurosci. 2017; 11:80. Published 2017 Mar 21. doi:10.3389/fncel.2017.00080

Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. Nat Neurosci. 2014; 17:17–23. *[*PMC free article*]* [PubMed] *[*Google Scholar*]*

van Es MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, et al. Amyotrophic lateral sclerosis. Lancet. 2017; 390:2084–2098. [PubMed] *[*Google Scholar*]*

Robberecht W, Philips T. The changing scene of amyotrophic lateral sclerosis. Nat Rev Neurosci. 2013; 14:248–264. [PubMed] *[*Google Scholar*]*

Blanco Y, Saiz A, Carreras E, Graus F. Changes of matrix metalloproteinase-9 and its tissue inhibitor (TIMP-1) after autologous hematopoietic stem cell transplantation in multiple sclerosis. J Neuroimmunol 2004; 153: 190-194.

Burk, K., & Pasterkamp, R. J. (2019). Disrupted neuronal trafficking in amyotrophic lateral sclerosis. Acta neuropathologica, 137(6), 859–877. https://doi.org/10.1007/s00401-019-01964-7

Silani V, Cova L, Corbo M, Ciammola A, Polli E. Stem-cell therapy for amyotrophic lateral sclerosis. Lancet 2004; 364: 200-202.

Vastag B. Stem cells step closer to the clinic: paralysis partially reversed in rats with ALS-like disease. JAMA 2001; 285: 1691-1693

Mazzini L, Fagioli F, Boccaletti R. Stem-cell therapy in amyotrophic lateral sclerosis. Lancet 2004; 364: 1936-1937.

De Bellis R, Cordoba A, Bello L. Treatment of 12 patients with ALS, grafting cells through neuroendoscopy. Bone Marrow Transplant 2006; 37 (Suppl 1): S133

Appel SH, Engelhardt JI, Henkel JS, Luo Y, Brenner MK, Popat UR. Allogeneic hematopoietic stem cell transplantation. 2004. Amyotroph Lateral Scler Other Motor Neuron Disor 2004; 5 (Suppl 2): 54

Fassas A, Kimiskidis VK. Stem cell transplantation for multiple sclerosis: what is the evidence? Blood Rev 2003; 17: 233-240.

Pachman, L. M., & Khojah, A. M. (2018). Advances in Juvenile Dermatomyositis: Myositis Specific Antibodies Aid in Understanding Disease Heterogeneity. The Journal of pediatrics, 195, 16–27. https://doi.org/10.1016/j.jpeds.2017.12.053

Statistical Office, Ministry of Finance, Economic Planning, Sustainable Development and Information Technology [Internet]. Statistical Office, Government of Saint Vincent and the Grenadines. 2019 [cited 15 July 2019]. Available from: http://stats.gov.vc/stats/

World Population Prospects - Population Division - United Nations [Internet]. Population.un.org. 2019 [cited 15 July 2019]. Available from: https://population.un.org/wpp/

Government of Saint Vincent and the Grenadines, 'Saint Vincent and the Grenadines HIV and AIDS National Strategic Plan, 2010–2014', Ministry of Health and the Environment, Kingstown, 2010

Government of Saint Vincent and the Grenadines, 'Education Sector Development Plan St. Vincent and the Grenadines 2012- 2017', Ministry of Education, Kingstown, DATE.

Government of Saint Vincent and the Grenadines, 'Saint Vincent and the Grenadines Educational Statistics Digest, 2014–2015', Ministry of Education, Kingstown, 2015a.

Government of Saint Vincent and the Grenadines, 'St. Vincent and the Grenadines Education for All 2015 Review', Education Research and Information Communication Technology Department, Ministry of Education, Kingstown, 2015b.

McGonagle D, McDermott MF (2006) A proposed classification of the immunological diseases. PLoS Med 3(8): e297. DOI: 10.1371/journal. pmed.0030297

McGonagle D, McDermott MF (2006) A Proposed Classification of the Immunological Diseases. PLoS Med 3(8): e297. https://doi.org/10.1371/journal.pmed.0030297

Warren et al, 2018.review of medical microbiology and immunology, a guide to clinical infectious diseases.15th edition, chapter 57 -61, page 475-530, Copyright © 2018 by McGraw-Hill Education.

S.B. Rosa, J.C. Voltarelli, J.A.B. Chies and P. Pranke Hawkins PN, Lachmann HJ, Aganna E, McDermott MF (2004) Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. Arthritis Rheum 50: 607–612.

McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW (1999) Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 97: 133–144. et al.

Strober W, Kitani A, Watababe T (2006) Signaling pathways and molecular interactions of NOD1 and NOD2. Nat Rev Immunol 6: 9–20.)

Hawkins PN, Lachmann HJ, Aganna E, McDermott MF (2004) Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. Arthritis Rheum 50: 607–612.

McGonagle D, McDermott MF (2006) A Proposed Classification of the Immunological Diseases. PLoS Med 3(8): e297. https://doi.org/10.1371/journal.pmed.0030297)

Witebsky E, Rose NR, Terplan K, Paine JR, Egan RW (1957). "Chronic thyroiditis and autoimmunization". *J. Am. Med. Assoc*. **164** (13): 1439–47. doi:10.1001/jama.1957.02980130015004. PMID 13448890)

Li, P., Zheng, Y., & Chen, X. (2017). Drugs for Autoimmune Inflammatory Diseases: From Small Molecule Compounds to Anti-TNF Biologics. *Frontiers in pharmacology*, *8*, 460. https://doi.org/10.3389/fphar.2017.00460)

Wahl C, Liptay S, Adler G, Schmid RM. Sulfasalazine: a potent and specific inhibitor of nuclear factor kappa B. *J Clin Invest*. 1998;101(5):1163- 1174. doi:10.1172/JCI992)

Fujita T, Kutsumi H, Sanuki T, Hayakumo T, Azuma T. Adherence to the preventive strategies for nonsteroidal anti-inflammatory drug- or low-dose aspirin-induced gastrointestinal injuries. *J Gastroenterol*. 2013;48(5):559- 573. doi:10.1007/s00535-013-0771-8).

Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*. 2016;7(1):e135. Published 2016 Jan 7. doi:10.1038/ctg.2015.63) Other possible reported side effects of anti-TNF are cancer, worsening condition in heart failure patient, development of multiple sclerosis and reactivation of latent tuberculosis.

Balakumar P, Singh M. Anti-tumor necrosis factor-alpha therapy in heart failure: future directions. *Basic Clin Pharmacol Toxicol*. 2006;99(6):391- 397. doi: 10.1111/j.1742-7843.2006.pto_508.x)

Robinson WH, Genovese MC, Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism: by what mechanisms could tumor necrosis factor alpha antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? *Arthritis Rheum*. 2001;44(9):1977- 1983. doi:10.1002/1529-0131(200109)44:9<1977: AID-ART345>3.0.CO;2-6)

Pasut G. Pegylation of biological molecules and potential benefits: pharmacological properties of certolizumab pegol. *BioDrugs*. 2014;28 Suppl 1: S15- S23. doi:10.1007/s40259-013-0064-z)

Desai RJ, Hansen RA, Rao JK, et al. Mixed treatment comparison of the treatment discontinuations of biologic disease-modifying antirheumatic drugs in adults with rheumatoid arthritis. *Ann Pharmacother*. 2012;46(11):1491- 1505. doi:10.1345/aph.1R203)

Mahal R. S. (2016). Stem Cells Applications in Regenerative Medicine and Disease Therapeutics. *International journal of cell biology*, *2016*, 6940283. https://doi.org/10.1155/2016/6940283)

Thomson M., Liu S. J., Zou L.-N., Smith Z., Meissner A., Ramanathan S. Pluripotency factors in embryonic stem cells regulate differentiation into germ layers. *Cell*. 2011;145(6):875–889. doi: 10.1016/j.cell.2011.05.017. [PMC free article] [PubMed] [CrossRef] [Google Scholar])

Fortier LA. Stem cells: classifications, controversies, and clinical applications. *Vet Surg*. 2005;34(5):415- 423. doi:10.1111/j.1532-950X.2005. 00063.x)

Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med*. 2003;348(7):593- 600. doi:10.1056/NEJMoa022287)

Petersdorf E. W., Malkki M., Gooley T. A., Martin P. J., Guo Z. MHC haplotype matching for unrelated hematopoietic cell transplantation. *PLoS Medicine*. 2007;4(1, article e8) doi: 10.1371/journal.pmed.0040008. [PMC free article] [PubMed] [CrossRef] [Google Scholar])

Thomson J. A. Embryonic stem cell lines derived from human blastocysts. *Science*. 1998;282(5391):1145–1147. doe: 10.1126/science.282.5391.1145. [PubMed] [CrossRef] [Google Scholar])This diverse lineage commitment remains the main reason why ESCs can be used in may diseases .In spinal cord injury it can be transplanted and noticeable improvement in balance, sensation and movement are seen

Shroff G., Gupta R. Human embryonic stem cells in the treatment of patients with spinal cord injury. *Annals of Neurosciences*. 2015;22(4):208–216. doi: 10.5214/ans.0972.7531.220404. [PMC free article] [PubMed] [CrossRef] [Google Scholar]) ESCs can be used age-related macular degeneration(ARMD) through genomic incorporation COCO gene during embryogenesis which can suppress of TGFβ, BMP and Wnt signaling pathways, and allows commitment of ESCs into cone cells.

Zhou S., Flamier A., Abdouh M., et al. Differentiation of human embryonic stem cells into cone photoreceptors through simultaneous inhibition of BMP, TGFβ and Wnt signaling. *Development*. 2015;142(19):3294–3306. doi: 10.1242/dev.125385. [PubMed] [CrossRef] [Google Scholar])

Shiba Y., Fernandes S., Zhu W.-Z., et al. Human ES-cell-derived cardiomyocytes electrically couple and suppress arrhythmias in injured hearts. *Nature*. 2012;489(7415):322–325. doi: 10.1038/nature11317. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Fernandes S., Chong J. J. H., Paige S. L., et al. Comparison of human embryonic stem cell-derived cardiomyocytes, cardiovascular progenitors, and bone marrow mononuclear cells for cardiac repair. *Stem Cell Reports*. 2015;5(5):753–762. doi: 10.1016/j.stemcr.2015.09.011. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Avior Y., Levy G., Zimerman M., et al. Microbial-derived lithocholic acid and vitamin K_2 drive the metabolic maturation of pluripotent stem cells-derived and fetal hepatocytes. *Hepatology*. 2015;62(1):265–278. doi: 10.1002/hep.27803. [PubMed] [CrossRef] [Google Scholar])

Bruin J. E., Saber N., Braun N., et al. Treating diet-induced diabetes and obesity with human embryonic stem cell-derived pancreatic progenitor cells and antidiabetic drugs. *Stem Cell Reports*. 2015;4(4):605–620. doi: 10.1016/j.stemcr.2015.02.011. [PMC free article] [PubMed] [CrossRef] [Google Scholar)

Salguero-Aranda C., Tapia-Limonchi R., Cahuana G. M. Differentiation of mouse embryonic stem cells towards functional pancreatic beta-cell surrogates through epigenetic regulation of Pdx1 by nitric oxide. *Cell Transplantation*. 2016 doi: 10.3727/096368916x691178. [PubMed] [CrossRef] [Google Scholar])

Cheng A., Kapacee Z., Peng J., et al. Cartilage repair using human embryonic stem cell-derived chondroprogenitors. *Stem Cells Translational Medicine*. 2014;3(11):1287–1295. doi: 10.5966/sctm.2014-0101. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Vedantham V. New approaches to biological pacemakers: links to sinoatrial node development. *Trends in Molecular Medicine*. 2015;21(12):749–761. doi: 10.1016/j.molmed.2015.10.002. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list]

Greggio C., De Franceschi F., Figueiredo-Larsen M., et al. Artificial three-dimensional niches deconstruct pancreas development in vitro. *Development*. 2013;140(21):4452–4462. doi: 10.1242/dev.096628. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Fuoco C., Rizzi R., Biondo A., et al. In vivo generation of a mature and functional artificial skeletal muscle. *EMBO Molecular Medicine*. 2015;7(4):411–422. doi: 10.15252/emmm.201404062. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Dominici M., Le Blanc K., Mueller I., et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8(4):315–317. doi: 10.1080/14653240600855905. [PubMed] [CrossRef] [Google Scholar])

Sharma A. K., Bury M. I., Marks A. J., et al. A nonhuman primate model for urinary bladder regeneration using autologous sources of bone marrow-derived mesenchymal stem cells. *STEM CELLS*. 2011;29(2):241–250. doi: 10.1002/stem.568. [PubMed] [CrossRef] [Google Scholar])

Sen B., Xie Z., Uzer G., et al. Intranuclear actin regulates osteogenesis. *STEM CELLS*. 2015;33(10):3065–3076. doi: 10.1002/stem.2090. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Lin B.-J., Wang J., Miao Y., et al. Cytokine loaded layer-by-layer ultrathin matrices to deliver single dermal papilla cells for spot-by-spot hair follicle regeneration. *Journal of Materials Chemistry B*. 2016;4(3):489–504. doi: 10.1039/c5tb02265g. [CrossRef] [Google Scholar] [Ref list])

Shahrokhi S., Menaa F., Alimoghaddam K., McGuckin C., Ebtekar M. Insights and hopes in umbilical cord blood stem cell transplantations. *Journal of Biomedicine and Biotechnology*. 2012;2012:11. doi: 10.1155/2012/572821.572821 [PMC free article] [PubMed] [CrossRef] [Google Scholar])

Rentas S., Holzapfel N. T., Belew M. S., et al. Musashi-2 attenuates AHR signaling to expand human haematopoietic stem cells. *Nature*. 2016;532(7600):508–511. doi: 10.1038/nature17665. [PMC free article] [PubMed] [CrossRef] [Google Scholar)

Mehta R. S., Rezvani K., Olson A., et al. Novel techniques for ex vivo expansion of cord blood: clinical trials. *Frontiers in Medicine*. 2015;2, article 89 doi: 10.3389/fmed.2015.00089. [PMC free article] [PubMed] [CrossRef] [Google Scholar])

Benavides O. M., Brooks A. R., Cho S. K., Petsche Connell J., Ruano R., Jacot J. G. In situ vascularization of injectable fibrin/poly (ethylene glycol) hydrogels by human amniotic fluid-derived stem cells. *Journal of Biomedical Materials Research Part A*. 2015;103(8):2645–2653. doi: 10.1002/jbm.a.35402. [PubMed] [CrossRef] [Google Scholar] [Ref list])

Wolfrum K., Wang Y., Prigione A., Sperling K., Lehrach H., Adjaye J. The LARGE principle of cellular reprogramming: lost, acquired and retained gene expression in foreskin and amniotic fluid-derived human iPS cells. *PLoS ONE*. 2010;5(10) doi: 10.1371/journal.pone.0013703.e13703 [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Leferink A. M., Chng Y. C., van Blitterswijk C. A., Moroni L. Distribution and viability of fetal and adult human bone marrow stromal cells in a biaxial rotating vessel bioreactor after seeding on polymeric 3D additive manufactured scaffolds. *Frontiers in Bioengineering and Biotechnology*. 2015;3, article 169 doi: 10.3389/fbioe.2015.00169. [PMC free article] [PubMed] [CrossRef] [Google Scholar])

Wagner J. E., Jr., Brunstein C. G., Boitano A. E., et al. Phase I/II trial of stemregenin-1 expanded umbilical cord blood hematopoietic stem cells supports testing as a stand-alone graft. *Cell Stem Cell*. 2016;18(1):144–155. doi: 10.1016/j.stem.2015.10.004. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Liu X., Zheng P., Wang X., et al. A preliminary evaluation of efficacy and safety of Wharton's jelly mesenchymal stem cell transplantation in patients with type 2 diabetes mellitus. *Stem Cell Research & Therapy*. 2014;5(2, article 57) doi: 10.1186/scrt446. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list)

Wang D., Li J., Zhang Y., et al. Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: A Multicenter Clinical Study. *Arthritis Research and Therapy*. 2014;16(2, article R79) doi: 10.1186/ar4520. [PMC free article] [PubMed] [CrossRef]

Chang M.-Y., Huang T.-T., Chen C.-H., Cheng B., Hwang S.-M., Hsieh P. C. H. Injection of human cord blood cells with hyaluronan improves postinfarction cardiac repair in pigs. *Stem Cells Translational Medicine*. 2016;5(1):56–66. doi: 10.5966/sctm.2015-0092. [PMC free article] [PubMed] [CrossRef] [Google Scholar])

Travlos G. S. Normal structure, function, and histology of the bone marrow. *Toxicologic Pathology*. 2006;34(5):548–565. doi: 10.1080/01926230600939856. [PubMed] [CrossRef] [Google Scholar])

Morizane R., Lam A. Q., Freedman B. S., Kishi S., Valerius M. T., Bonventre J. V. Nephron organoids derived from human pluripotent stem cells model kidney development and injury. *Nature Biotechnology*. 2015;33(11):1193–1200. doi: 10.1038/nbt.3392. [PMC free article] [PubMed] [CrossRef] [Google Scholar])

DiGiusto D. L., Stan R., Krishnan A., Li H., Rossi J. J., Zaia J. A. Development of hematopoietic stem cell based gene therapy for HIV-1 infection: considerations for proof of concept studies and translation to standard medical practice. *Viruses*. 2013;5(11):2898–2919. doi: 10.3390/v5112898. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Herrera-Carrillo E., Berkhout B. Bone marrow gene therapy for HIV/AIDS. *Viruses*. 2015;7(7):3910–3936. doi: 10.3390/v7072804. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Lukashyk S. P., Tsyrkunov V. M., Isaykina Y. I., et al. Mesenchymal bone marrow-derived stem cells transplantation in patients with HCV related liver cirrhosis. *Journal of Clinical and Translational Hepatology*. 2014;2(4):217–221. doi: 10.14218/jcth.2014.00027. [PMC free article] [PubMed] [CrossRef] [Google Scholar])

Takahashi K., Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663–676. doi: 10.1016/j.cell.2006.07.024. [PubMed] [CrossRef] [Google Scholar])

Howden S. E., Maufort J. P., Duffin B. M., Elefanty A. G., Stanley E. G., Thomson J. A. Simultaneous reprogramming and gene correction of patient fibroblasts. *Stem Cell Reports*. 2015;5(6):1109–1118. doi: 10.1016/j.stemcr.2015.10.009. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list

Mahla R. S. (2016). Stem Cells Applications in Regenerative Medicine and Disease Therapeutics. *International journal of cell biology, 2016*, 6940283. https://doi.org/10.1155/2016/6940283)

Wilson A. A., Ying L., Liesa M., et al. Emergence of a stage-dependent human liver disease signature with directed differentiation of alpha-1 antitrypsin-deficient iPS cells. *Stem Cell Reports*. 2015;4(5):873–885. doi: 10.1016/j.stemcr.2015.02.021. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Zhu S., Russ H. A., Wang X., et al. Human pancreatic beta-like cells converted from fibroblasts. *Nature Communications*. 2016;7 doi: 10.1038/ncomms10080.10080 [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list])

Ringe J, Sittinger M. Tissue engineering in the rheumatic diseases. Arthritis Res Ther. 2009;11(1):211. [PMC free article] [PubMed] [Google Scholar])

Hayward K, Wallace CA. Recent developments in anti-rheumatic drugs in pediatrics: treatment of juvenile idiopathic arthritis. Arthritis Res Ther. 2009;11(1):216. [PMC free article] [PubMed] [Google Scholar])

Moore J, Brooks P, Milliken S, et al. A pilot randomized trial comparing CD34-selected versus unmanipulated hemopoietic stem cell transplantation for severe, refractory rheumatoid arthritis. *Arthritis Rheum*. 2002;46(9):2301- 2309. doi:10.1002/art.10495)

Moore J, Brooks P, Milliken S, et al. A pilot randomized trial comparing CD34-selected versus unmanipulated hemopoietic stem cell transplantation for severe, refractory rheumatoid arthritis. *Arthritis Rheum*. 2002;46(9):2301- 2309. doi:10.1002/art.10495)

Verburg RJ, Kruize AA, van den Hoogen FH, et al. High-dose chemotherapy and autologous hematopoietic stem cell transplantation in patients with rheumatoid arthritis: results of an open study to assess feasibility, safety, and efficacy. *Arthritis Rheum*. 2001;44(4):754- 760. doi:10.1002/1529-0131(200104)44:4<754::AID-ANR131>3.0.CO;2-N)

Snowden JA, Passweg J, Moore JJ, et al. Autologous hemopoietic stem cell transplantation in severe rheumatoid arthritis: a report from the EBMT and ABMTR. *J Rheumatol*. 2004;31(3):482- 488.

Jayne D, Passweg J, Marmont A, Farge D, Zhao X, Arnold R, et al. Autologous stem cell transplantation for systemic lupus erythematosus. Lupus 2004; 13: 168-176.

Burt RK, Traynor A, Statkute L, Barr WG, Rosa R, Schroeder J, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. JAMA 2006; 295: 527-535.)

Moore KA, Lemischka IR. Stem cells and their niches. *Science*. 2006 Mar 31;311(5769):1880-5. Review.)

Fassas A, Kimiskidis VK. Stem cell transplantation for multiple sclerosis: what is the evidence? Blood Rev 2003; 17: 233-240. 27

Fassas A, Passweg JR, Anagnostopoulos A, Kazis A, Kozak T, Havrdova E, et al. Hematopoietic stem cell transplantation for multiple sclerosis. A retrospective multicenter study. J Neurol 2002; 249: 1088-1097.

Martini, G., Biscaro, F., Boscaro, E., Calabrese, F., Lunardi, F., Facco, M., Agostini, C., Zulian, F., & Fadini, G. P. (2015). Reduced levels of circulating progenitor cells in juvenile idiopathic arthritis are counteracted by anti TNF-α therapy. *BMC musculoskeletal disorders*, *16*, 103. https://doi.org/10.1186/s12891-015-0555-9)

Brinkman DM, de Kleer IM, ten Cate R, et al. Autologous stem cell transplantation in children with severe progressive systemic or polyarticular juvenile idiopathic arthritis: long-term follow-up of a prospective clinical trial. *Arthritis Rheum*. 2007;56(7):2410-2421. doi:10.1002/art.22656)

Voltarelli JC, Stracieri ABPL, Oliveira MCB, Godoi DF, Moraes DA, Pieroni F. Transplante de células tronco hematopoéticas em doenças reumáticas. Parte 2: Experiência brasileira e perspectivas futuras. Rev Bras Reumatol 2005; 45: 301-312.

Kumar, V., Fausto, N., Abbas, A., Cotran, R., & Robbins, S. (2004). *Robbins and Cotran's pathologic basis of disease* (10th ed., pp. 171-240). Elsevier Saunders.

Levinson, W., Joyce, E., Nussbaum, J., Schwartz, B., & Chin-Hong, P. (2020). *Review of Medical Microbiology & Immunology* (16th ed., pp. 10-250). McGraw-Hill Education LLC.

APPENDIX 1
DATA EXTRACTION TOOL

Socio-Demographics

Year

- 2014
- 2015
- 2016
- 2017
- 2018
- 2019
- 2020

Case file No

_____

Diseases Code number
example; B7-10

_____

Sex

- Male
- Female

Age

APPENDIX 2
ETHICAL APPROVAL

MINISTRY OF HEALTH,
WELLNESS AND THE
ENVIRONMENT
Ministerial Building, Kingstown,
Saint Vincent and the Grenadines

IRB#: MOHWE120220

February 12th, 2020

Okikiade Adedeji
Principal Investigator
All Saints University
St, Vincent and the Grenadines

Dear Okikiade Adedeji

ETHICS APPROVAL: THE INSIGHT ON PREVALENCE, INCIDENCE AND PERSPECTIVE OF IMMUNOLOGICAL DISEASE CARIBBEAN (ST VINCENT AND THE GRENADINES IN VIEW) FROM 2016-2020

I refer to your research proposal of re: the subject at caption and write to advise you that the approval has been granted for the aforementioned research project. **You are required to request permission from the Hospital Administrator, Milton Cato Memorial Hospital, to gain access to the relevant hospital records.**

Please be advised that you are required to submit a summary report of the project to the Ministry of Health, Wellness and the Environment Research Ethics Committee.

In the event that any changes are anticipated, you must notify the National Research Ethics Committee to seek permission to make such changes before you proceed.

CHIEF MEDICAL OFFICER

for Dr. Simone Keizer-Beache
Chief Medical Officer

TEL. 784 457 2586 FAX. 784 457 2684
email: mohesvg@gmail.com/mohesvg@gov.vc