An Approach to Determine the Prevalence and Factors Associated with Prediabetes and diabetes mellitus among young adults

A Dissertation Submitted to East West University's Department of Pharmacy in Partial Fulfillment of the Requirement for the Degree of Bachelor of Pharmacy B. PHRM THESIS

Submitted By:

Tasnimul Hossain Majumder

Id: 2019-1-70-059

Declaration by the Candidate

I, Tasnimul Hossain Majumder, hereby declare that the dissertation entitled **"An Approach to Determine the Prevalence and Factors Associated with Prediabetes and diabetes mellitus among young adults"** submitted by me to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the award of the degree of Bachelors of Pharmacy is a complete record of original research work carried out by me during the year 2022 of our research in the Department of Pharmacy, East West University, under the supervision and guidance of Zasharatul Islam, Senior Lecturer, Department of Pharmacy, East West University. The thesis has not formed the basis for the award of any other degree/ diploma/ fellowship or other similar titles to any candidate of any university.

Tasnimul Hossain Majumder

ID: 2019-1-70-059

Department of Pharmacy,

East West University, Dhaka - 1212

Certification by the Supervisor

This is to certify that the thesis entitled "**An Approach to Determine the Prevalence and Factors Associated with Prediabetes and diabetes mellitus among young adults**" submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, was carried out by Tasnimul Hossain Majumder Id: 2019-1-70-059 under the supervision and guidance of me. The thesis has not formed the basis for the award of any other degree/diploma/fellowship or other similar titles to any candidate of any university.

_____

Zasharatul Islam

Senior Lecturer and Supervisor

Department of Pharmacy,

East West University, Dhaka-1212

Endorsement by the Chairperson

This is to certify that the thesis entitled "**An Approach to Determine the Prevalence and Factors Associated with Prediabetes and diabetes mellitus among young adults**" submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy, was carried out by Tasnimul Hossain Majumder Id: 2019-1-70-059.

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Dr. Sufia Islam

Professor & Chairperson

Department of Pharmacy East West University, Dhaka-1212

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Tasnimul Hossain Majumder

Dedication

This research paper is dedicated to My beloved Parents and My Family Members

Table of Content

Chapter -1: Introduction

Chapter-2: Literature Review

List of Figures

List of Tables

Abbreviation

ADHD	Attention Deficit Hyperactivity Disorder
CVD	Cardiovascular Disease

CI	Confidence of Interval
OD	Odds Ratio
p-value	Probability value
RT	Reaction Time
MS	Milliseconds
CIDI	Composite International Diagnostic Interview
WHO	World Health Organization
IoT	Internet of Things
LED	Light-emitting diode
RF-EMR	Radio-frequency Electromagnetic radiation fields
RF	Radiofrequency
SCWT	Stroop Color and Word Test
VDT	Visual Display Terminal
SEBR	Spontaneous eye blink rate
SD	Standard Deviation
IDF	The International Diabetes Federation

Abstract

To see if berberine is effective and safe in the treatment of prediabetes. Methods. On the treatment of T2DM, randomized studies of berberine against lifestyle change, placebo, and/or oral hypoglycemics intervention were included. Two reviewers independently retrieved study population characteristics and outcome outcomes. For the data that was available, meta-analyses were conducted. Results. This analysis includes 14 randomized trials with a total of 153 individuals. The quality of the methodology was often poor. The cointervention of berberine with lifestyle modification demonstrated a considerably hypoglycemic and anti-dyslipidemia effect when compared to lifestyle modification with or without placebo. Berberine did not exhibit a substantial improvement in glycemic control when compared to oral hypoglycemics such as metformin, glipizide, or rosiglitazone, although it did have a moderate antidyslipidemia benefit. In T2DM, hyperglycemia and dyslipidemia are common. However, because of the low methodological quality, small sample size, limited number of trials, and unknown bias concerns, the evidence for berberine in the treatment of T2DM should be regarded with caution. Patients with prediabetes who do not follow their treatment regimens are more likely to have negative results. Clinicians and health-care institutions are increasingly focused on improving drug adherence. We investigate the discrepancies in patient and provider perceptions of medication adherence obstacles in prediabetic patients.

Chapter 1

Introduction

1.Introduction

1.1 Diabetes:

Correct the Justification in every page

Diabetes is a long-term illness that affects the way your body converts food into energy.

The majority of the food you consume is converted to sugar (also known as glucose) and released into your bloodstream. Your pancreas releases insulin when your blood sugar levels rise. Insulin is a key that allows blood sugar to enter cells and be used as energy.

If you have diabetes, your body either does not produce enough insulin or does not utilize it as effectively as it should. Too much blood sugar persists in your bloodstream when there isn't enough insulin or when cells stop responding to insulin. This can lead to major health issues like heart disease, eyesight loss, and renal illness over time. Although there is no cure for diabetes, decreasing weight, eating healthy foods, and exercising can all help. Taking medication as needed, receiving diabetes self-management education and support, and keeping health-care appointments can all help to lessen the impact diabetes has on your life. (1)

In 2005, it was estimated that more than 20 million people in the United States had diabetes. Approximately 30% of these people had undiagnosed cases. Increased risk for diabetes is primarily associated with age, ethnicity, family history of diabetes, smoking, obesity, and physical inactivity. Diabetes-related complications—including cardiovascular disease, kidney disease, neuropathy, blindness, and lower-extremity amputation—are a significant cause of increased morbidity and mortality among people with diabetes, and result in a heavy economic burden on the US health care system. With advances in treatment for diabetes and its associated complications, people with diabetes are living longer with their condition. This longer life span will contribute to further increases in the morbidity associated with diabetes, primarily in elderly people and in minority racial or ethnic groups. In 2050, the number of people in the United States with diagnosed diabetes is estimated to grow to 48.3 million. Results from randomized controlled trials provide evidence that intensive lifestyle interventions can prevent or delay the onset of diabetes in high-risk individuals. In addition, adequate and sustained control of blood sugar levels, blood pressure, and blood lipid levels can prevent or delay the onset of diabetes-related complications in people with diabetes. Effective interventions, at both the individual and population levels, are desperately needed to slow the diabetes epidemic and reduce diabetes-

related complications in the United States. This report describes the current diabetes epidemic and the health and economic impact of diabetes complications on individuals and on the health care system. The report also provides suggestions by which the epidemic can be curbed. (2)

The International Diabetes Federation (IDF) estimates that 19.8 million people have diabetes in Africa where approximately 75% are still undiagnosed. Prediabetes contributes up to 90% of all cases of diabetes (World Health Organization. WHO | Diabetes fact sheet. 2016). The increase in diabetes prevalence in sub-Saharan Africa (SSA) has grown in parallel with the increase in obesity and other cardiovascular risk factors. Countries with the highest estimated numbers of persons with diabetes include Nigeria (3.9 million), South Africa (2.6 million), Ethiopia (1.9 million), and Tanzania (1.7 million) . Diabetes exerts a huge societal burden by reducing quality of life and life expectancy, as well as causing economic loss to individuals and nations

Rapid urbanization, increasingly sedentary lifestyles, and unhealthy eating habits have contributed largely to the increased prevalence of diabetes, estimated to be 5.7% and expected to rise to 6% by 2035 (International Diabetes Federation. IDF diabetes atlas. 6th ed. 2013;). The prevalence of pre-diabetes, a transition stage with blood glucose levels higher than normal but not high enough to be diagnosed as diabetes, is currently at 8.3% and expected to rise to 9.3% by 2035. Therefore, interventions to control the epidemic of diabetes and hyperglycemia-related vascular complications should start at this early stage of its development Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: results from the Diabetes Prevention Program outcomes study.

The prevalence of diabetes in Tanzania and Uganda, two SSA countries with comparable socioeconomic status, is estimated at 7.8% (Tanzania) and 4.1% (Uganda), while impaired glucose tolerance is estimated at 9.1% in Tanzania and 6.6% in Uganda. The estimated number of undiagnosed patients is 469.3 per 1,000 and 1281.7 per 1,000 in Uganda and Tanzania, respectively .The health delivery service structure for Tanzania and Uganda is pyramidal with primary health care services at its base. Despite policy stating that primary care facilities should provide services for diabetes, studies have demonstrated that most dispensaries and health centers do not provide such services. Lack of guidelines, basic supplies, diagnostic tools, and training are the frequently cited reasons for the underutilization of primary health care in providing diabetes care

Although communicable diseases remain the most common causes of morbidity and mortality in low-income countries, the rapid increase in the prevalence of non-communicable diseases (NCDs) including diabetes creates a challenge for prevention and treatment. Data for diabetes in SSA are sparse and often from single-country studies. Lack of comprehensive studies on diabetes etiology and risk factors creates a knowledge gap.There is an urgent need to obtain local data in order to implement locally applicable preventive strategies.

We report on data from the Africa/HSPH Partnership for Cohort Research and Training (PACT), an initiative that aims to conduct a large prospective study in South Africa, Tanzania, Uganda, and Nigeria to gain knowledge on risk factors for NCDs including diabetes. The aim of this analysis from pilot studies was to determine the prevalence of diabetes and pre-diabetes and its associated risk factors in Tanzania and Uganda (5)

1.2 Pre-diabetes:

Pre-diabetes (intermediate hyperglycemia) is a high-risk diabetes state characterized by glycemic variables that are greater than normal but below diabetes thresholds. Every year, 5–10% of people with pre-diabetes develop diabetes, with the same percentage returning to normal glucose levels. Pre-diabetes is becoming more common around the world, with scientists predicting that by 2030, more than 470 million individuals will have the disease. Pre-diabetes is linked to the presence of both insulin resistance and -cell dysfunction—abnormalities that begin before glucose levels alter. Pre-diabetes is linked to early types of nephropathies, chronic kidney disease, small fiber neuropathy, diabetic retinopathy, and an elevated risk of macrovascular disease, according to observational research. In addition to glycemic values, multifactorial risk scores employing noninvasive measures and blood-based metabolic characteristics. (3)

China has the world's largest diabetes epidemic, which continues to increase. The prevalence of diabetes in China was reported to be 0.67% in 1980 and 11.6% in the latest published nationwide estimate in 2010. Moreover, according to the 2010 survey, the prevalence of prediabetes was 50.1%, implying that approximately 500 million Chinese adults may have had prediabetes. However, this high estimate for prediabetes raised concern over the possibility of an overestimation.[6] As a disorder of glucose metabolism, diabetes mellitus affects multiple organ systems and is associated with a variety of vascular and several nonvascular complications. Ongoing reliable estimations are needed to plan effective national prevention and treatment programs for diabetes management.

In addition, although a few epidemiologic studies were available to estimate the prevalence of diabetes among different ethnic groups in China, the data were from different studies conducted at different times. Direct comparison under a consistent survey design is therefore of importance for policy making for diabetes management in Chinese minorities.

This study was conducted to provide more recent estimates of the prevalence of diabetes and prediabetes in China and to investigate their ethnic pattern, using a nationally representative survey conducted in 2013. (4)

1.3 Pre-diabetes Ranges:

The prevalence rate of adult diabetes status by quartiles of baseline childhood FPG levels revealed a negative trend for prediabetes (P.001) and diabetes (P =.03), with an apparent threshold occurring at or beyond the 50th percentile (86 mg/dL). The area under the receiver operating curve analysis for the predictive value of the above threshold yielded a C value of 0.855 for prediabetes and 0.789 for diabetes models, with sensitivity and specificity of 76.9% and 85.2 percent for prediabetes and 75.0 percent and 76.0 percent for diabetes, respectively. Individuals with elevated childhood FPG levels were 3.40 times more likely to acquire prediabetes (P.001) in a multivariate analysis that included anthropometric, hemodynamic, and metabolic characteristics from childhood to adulthood, as well as baseline childhood FPG status (vs 50th percentile). As adults, they are 2.06 times more likely to develop diabetes (P =.05).

The fact that elevated FPG level in childhood, even within the normoglycemic range, is a predictor of Prediabetes in younger adulthood has implications for health care policy.

While 19 million people have Prediabetes mellitus, 54 million individuals show impaired fasting glucose as adults, which may represent a prediabetic state It is also recognized that cardiovascular morbidity and mortality risks are elevated in individuals with relatively increased fasting plasma glucose (FPG) levels within the reference range

The American Diabetes Association (ADA) has lowered the diagnostic cutoff point for impaired fasting glucose from 110 mg/dL to 100 mg/dL (to convert to millimoles per liter, multiply by 0.0555) to improve prediction of prediabetes However, the current criteria for diagnosis of

prediabetes set by the ADA are not age specific. Studies have recently demonstrated that higher plasma glucose levels within the normoglycemic range might be a predictor of diabetes, although it raises controversy regarding the implications for health care policy. Further, FPG and the prevalence of impaired carbohydrate metabolism are known to increase with age. Also, glycated hemoglobin, an indicator of long-term glucose homeostasis, is positively correlated with age in nondiabetic populations, even after eliminating individuals with impaired FPG and/or impaired glucose tolerance. Although the association between fasting glucose levels in the reference range and prediabetes mellitus has been described on single baseline measurements for younger adults and older age groups such data on long-term, longitudinal, and progressive changes in the cardiometabolic risk variables from childhood to younger adulthood are scant. This study examined the prediction of normal FPG levels for the development of prediabetes for a 21-year period beginning in childhood. (6)

1.4 Impact:

In observational registries and randomized clinical studies, the independent predictive impact of diabetes mellitus (DM) and prediabetes mellitus (perm) on mortality outcomes in patients with chronic heart failure has been examined, but the results have been ambiguous or contradictory.

Chronic heart failure (CHF) is a gradual, complex clinical syndrome with high rates of morbidity and mortality that occurs as a result of a wide range of cardiovascular impairments, either alone or in conjunction with other concomitant disorders like diabetes mellitus (DM), resulting in early death. Diabetes mellitus (DM) is particularly common in people with heart failure (HF), with up to 40%–45% of these patients having it. Not surprisingly, the burden of morbidity and death associated with CHF and DM has posed a significant challenge to the long-term viability of modern healthcare systems. (7)

1.4.1: Impact of Diabetes on Cardiovascular Disease:

Several clinical trials have studied the effect of intense hyperglycemia treatment on cardiovascular risk reduction in both T2D [22–25] and T1D in recent decades, with mixed results. The clinical characteristics of the examined populations, such as the presence of CVD and the length of diabetes, as well as the type of intensive intervention used and the desired outcomes, all contribute to the disparities in the outcomes.

In the *United Kingdom Prospective Diabetes Study* (UKPDS), in newly diagnosed T2D patients, the early intensive treatment of hyperglycemia within the first five years of disease resulted in a long-term cardiovascular benefit, compared with patients in the conventional treatment group. This benefit was observed even after the loss of difference in glycemic control between the groups that occurred during the further five years of observational followup. However, the same was not observed in the three other large clinical trials conducted in patients with T2D. In the *Veterans Affairs Diabetes Trial* (VADT), older patients with 10 years mean duration of diabetes had no cardiovascular benefit when submitted to an intensive glycemic control regimen. This population comprised 40% of patients with a previous history of cardiovascular disease. Similar results were obtained from the *Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation* (ADVANCE) trial which aimed to achieve an A1c of 6.5% through intensive treatment with gliclazide plus other drugs. This strategy did not reduce the rate of major macrovascular events or death, despite a reduction in the incidence of diabetic nephropathy. As in VADT, patients were older (mean age of 66 years) and had a longer duration of diabetes (8 years) than UKPDS patients when the intensive treatment was started. In contrast, more strict intensive treatment aiming to reduce HbA1c below 6% in T2D patients, as occurred in the *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) trial in addition to showing no benefit in reducing macrovascular events resulted in increased mortality, weight gain, and risk of hypoglycemia. Patients in this study presented a high cardiovascular risk profile when first initiated intensive glycemic treatment. Table 1 presents the main differences between these trials.

In T1D patients, *the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications* (DCCT/EDIC) study showed the cardiovascular benefits of an intensive glycemic control after a followup of 17 years. The patients in this study were treated intensively for about 6.5 years and followed for 10 years observationally. Even after losing the strict glycemic control, represented by a glycated hemoglobin level below 7%, during the observational period, the group previously intensively treated presented a reduction of any cardiovascular event by 42%.

The main lesson learned from these results is that intensive treatment of hyperglycemia, targeting glycated hemoglobin levels below 7%, when initiated early in patients with short duration of diabetes and low cardiovascular risk, results in cardiovascular benefits. The same is not true when looking up tighter glycemic targets in older patients exposed to hyperglycemia for years before and with a higher cardiovascular risk profile.

This early protection is postulated to result from a mechanism known as "metabolic memory," which means that the effect of the early glycemic exposure environment is remembered later in target organs resulting in long-term deleterious or protective effects. The mechanisms involved in this process appear to comprehend epigenetic changes and intracellular metabolic changes that result in oxidative stress, low-grade inflammation, and endothelial dysfunction (Figure 1). These topics will be discussed below.

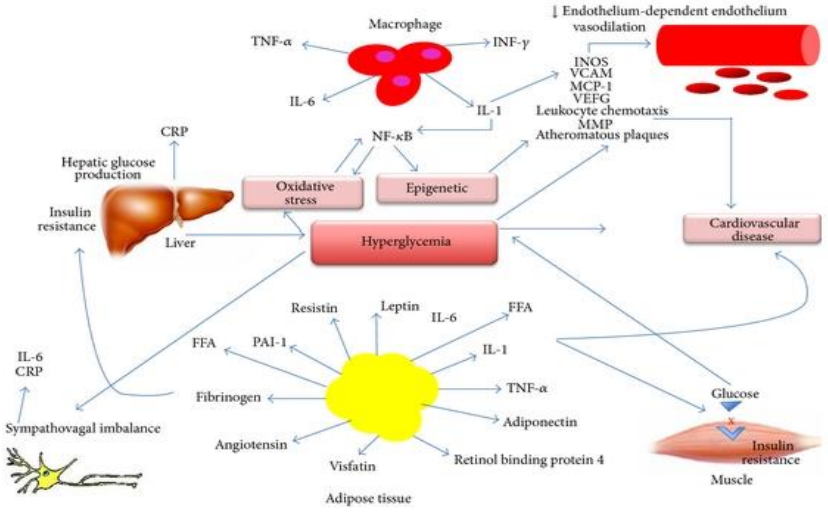

Figure 1.1: Pathogenesis of cardiovascular disease in diabetes:

The mechanisms involved in the pathogenesis of cardiovascular disease in diabetes comprehend epigenetic changes and intracellular metabolic changes that result in oxidative stress, low-grade inflammation, and endothelial dysfunction. CRP: C-reactive protein; FFA: free fatty acids; INOS: inducible nitric oxide synthase; IL-1: interleukin 1; IL-6: interleukin 6; MCP-1: monocyte chemoattractant molecule 1; MMP: matrix metalloproitenase; NF-κB: nuclear factor kappa-β; PAI-1: plasminogen activator inhibitor-1; VCAM-1; vascular cell adhesion molecule-1; VEFG: vascular endothelial growth factor; TNF-α: Tumor necrosis factor-α; INF-γ: Interferon-γ.

Obesity:

Obesity, which prevalence is also increasing worldwide is becoming a major public health issue due to its association with chronic diseases such as diabetes mellitus, hypertension, dyslipidemia, sleep apnea, osteoarticular disease, and cardio and cerebrovascular diseases. According to data from the WHO in 2008, the global prevalence of obesity (body mass index (BMI) $\geq 30\ kg/m^2$) was 10% in men and 14% in women. Data from the National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of overweight and obesity in adults increased from 55.9% to 64.5% and from 22.9% to 30.5%, from 1988–1994 to 1999-2000, respectively.

Obesity, especially with visceral fat deposition, is associated with low-grade inflammation, which plays a role in the pathogenesis of diabetes, and both diseases are associated with significant increase in morbidity and mortality due to CVD.

The main determinants for the onset of diabetes are beyond genetic factors, obesity and sedentary lifestyle. Several studies have shown decreased incidence of diabetes by nonpharmacologic treatments, lifestyle changes, and body weight reduction. The Finish Diabetes Prevention Study Group showed that the incidence of diabetes was reduced in 58% in the group with only intensive lifestyle changes. The Diabetes Prevention Program (DPP), diabetes incidence was reduced by 58% with intensive lifestyle intervention when compared to placebo and remained reduced by 34% after 10 years of followup . Therefore, efforts should be made to encourage the adoption of healthy lifestyle and thus to combat the obesity epidemic.

Dyslipidemia:

Dyslipidemia in T2D worsens cardiovascular risk due to the peculiar atherogenic profile composed by increased very low-density lipoprotein (VLDL) cholesterol, triglycerides and small and dense LDL cholesterol levels and decreased high-density lipoprotein (HDL) cholesterol levels. With such lipoproteins modified by oxidation and glycosylation there is a reduction on vascular compliance predisposing to early and aggressive atherosclerosis. This may also occur in T1D, even though they are young patients and seldom present lipid abnormalities, but in this case, the atherogenic profile is not caused exclusively by increased lipid levels, and hyperglycemia *per se* is also pivotal in this process. This was evidenced in an experimental study which concluded that either diabetic hyperlipidemia or hyperglycemia accelerates distinct phases

of atherogenesis in diabetes. In this study, it was shown that the dyslipidemia associated with diabetes is not sufficient to initiate the atherosclerotic lesion, because the progression of atherosclerosis process could be normalized after intensive glycemic control with insulin in mice.

In many interventional studies, the reduction of LDL cholesterol and triglycerides and increase of HDL cholesterol have been proved to be effective in reducing macrovascular disease and mortality in patients with T2D, especially in those with previous CAD.

The *Collaborative Atorvastatin Diabetes Study* (CARDS) was the first trial that studied T2D patients without previous CVD. Intervention with atorvastatin 10 mg showed 37% reduction in Cardiovascular events and 48% reduction in stroke when compared to placebo. In the *HDL Atherosclerosis Treatment Study* (HATS), the combined use of low doses of simvastatin (10 to 20 mg/day) with high doses of niacin (2 to 4 g/day) showed a reduction in absolute risk of 13% for cardiovascular outcomes when HDL reached the target. The study TNT (treatment to new targets) studied patients with T2D with previous CVD and compared the use of Atorvastatin 10 mg (conventional group) with Atorvastatin 80 mg (intensive group), and the goals were 100 mg and 80 mg for LDL cholesterol, respectively. The aggressive target achieved in this study (1.9 mmol/L) showed the most reduced rates of mortality due to cardiovascular events among all studies with statins.

Although decreasing LDL cholesterol has brought enough and established evidence on reducing cardiovascular mortality in prediabetes if the treatment of dyslipidemia starts too late it may not be effective in avoiding atherosclerosis progression. According to the Deutsche Diabetes Dialyze Study (4D) that studied 1,255 T2D patients with end-stage renal disease which were randomized to Atorvastatin 20 mg/day or matching placebo duringfour years, there was no significant reduction in cardiovascular events with the intervention when compared to placebo. Concerning cholesterol goals for diabetics, as far as we know, we should get as lower cholesterol levels as possible as stated by National Cholesterol Education Program Adult Treatment Panel III Guidelines (NCEP ATP III) . It is well established that diabetic subjects are considered to belong to a high-risk category, thus their benefit from LDL-lowering therapy appears when LDL-C goal of 1.8 mmol/L is achieved.

In a recent meta-analysis which reviewed 22 trials with statins versus control, it was showed that statin use could be associated with an increased incidence of diabetes. Despite the fact that an immediate doubling in cardiovascular risk in individuals with 5-year risk of major vascular

events lower than 10%, such an effect is more than 50-times smaller than the absolute benefit observed with statin therapy in such individuals (about 11 fewer major vascular events per 1,000 treated over 5 years per 1.0 mmol/L reduction in LDL cholesterol).

Considering hypertriglyceridemia, there is little evidence to support the benefits the goals to be achieved can bring. Fibrates are recommended to reduce pancreatitis risk in patients with triglycerides levels above 4.5 mmol/L when lifestyle modification does not succeed. Until recently, there were no data that support that the combined use of statins and fibrates could reduce cardiovascular mortality. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multinational randomized trial conducted with 9,795 patients with T2D which showed that fenofibrate did not significantly reduce the risk of the primary outcomes of coronary events. Instead, it reduced the number of total cardiovascular events (fewer nonfatal myocardial infarctions and revascularizations) . Another message from this study was that fibrate confers microvascular protection, because it reduced the need for laser treatment for diabetic retinopathy.

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5. Hypertension

Hypertension is a highly prevalent disease worldwide and very common among patients with diabetes. Approximately from 10 to 30% of T1D and 60% of T2D patients have hypertension.

The coexistence of these two conditions increasesthe risk of developing macrovascular complications (myocardial infarction, stroke) and also microvascular complications (nephropathy and retinopathy). The vigorous treatment of hypertension may reduce the progression of these complications.

The time hypertension starts differs in different types of diabetes. In patients with T1D, hypertension develops years after diagnosis usually already reflecting the development of diabetic nephropathy. Blood pressure (BP) tends to increase three years after the onset of microalbuminuria. In patients with prediabetes, hypertension may be present at diagnosis or even before the elevation of blood glucose levels. The association between hypertension and obesity is well established leading to a higher rate of cardiovascular morbidity and mortality in patients with these two conditions.

The recommended target blood pressure for patients with diabetes, according to the ADA is characterized by BP < 130/80 mmHg. Although, the European Society of Hypertension Task

Force states that BP goals traditionally recommended in diabetes are not supported by outcomes evidence from trials. They also reinforce only to pursue a reasonable BP reduction without indicating a goal which is unproven, since it has also been very difficult to achieve blood pressure goals in the majority of the patients.

According to the ADVANCE study in diabetic patients at high cardiovascular risk lower BP levels should be reached. One should always take into consideration the individualization of treatment and its correlation with response to therapy, drug tolerance, and individual characteristics. However, randomized clinical trials have demonstrated that the established therapeutic target (BP < 130/80 mmHg) own benefits in reducing CHD, stroke, and kidney disease. In patients with renal insufficiency and proteinuria above 1 to 2 g per day, the target BP should approach 120/75 mmHg.

The treatment of hypertension in diabetic patients aims at the prevention of CVD, minimizing the progression of renal disease and diabetic retinopathy. According to the UKPDS, patients with T2D may benefit more from tight control of BP than with strict control of blood glucose levels. Initial treatment should include nonpharmacological measures such as weight reduction (in overweight and obesity), regular exercising, reducing salt intake (<1500 mg per day), avoiding excessive alcohol consumption (no more than two servings per day in men and no more than one serving per day in women), and smoking cessation. Pharmacological therapy should be initiated in all diabetics who persist with BP > 130/80 mmHg, when a change in lifestyle has already been implemented for 3 months or when the maximum BP levels are already higher than 140/90 mmHg at diagnosis.

Pharmacological therapy can be accomplished with various classes of antihypertensive agents. Diuretics, angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta blockers, calcium channel blockers, alpha blockers, and combination of blockers of the renin-angiotensin have shown to be effective in reducing cardiovascular events. In most cases, the association of two or three drugs may be necessary in order to achieve the goals of the treatment.

The ACCORD-BP study, evaluating more intensive treatment of blood pressure (systolic blood pressure reduction aiming at levels lower than 120 mmHg) in patients with T2D and CVD or at least two cardiovascular risk factors, showed no reduction in cardiovascular events rates (myocardial infarction, CHF, and cardiovascular death), although it was observed a reduction in the number of strokes.

Oxidative Stress

Increased intracellular glucose concentrations result in the activation of alternative pathways of metabolism such as the hexosamine and the aldose reductase pathways, both involved in the pathophysiology of chronic complications of diabetes. These pathways trigger an increased production of reactive oxygen species (ROS) and depletes substrates for important antioxidant enzymes. Additionally, increased intracellular glucose leads to the formation of advanced glycation end products (AGES) and the activation of protein kinase C (PKC). All these mechanisms lead to a common effect, an increased oxidative stress state.

Oxidative stress results from an imbalance between the production of ROS and the antioxidant defense. The ROSs are chemically instable and highly reactive molecules continuously produced by aerobic organisms that function as second messengers regulating the expression of redox signal sensitive genes (e.g., nuclear factor kappa-β (NFκ-B) gene) and in the production of inflammatory mediators. They are generated from enzymes that use oxygen as electron acceptor including the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, nitric oxide synthase (NOS), xanthine oxidase, the mitochondrial chain electron transport, lipoxygenase, cyclooxygenase, and cytochrome P450. The first three are the main sources of ROS in the vascular wall.

The active form of NADPH oxidase is responsible for the reduction of the molecular oxygen resulting in the formation of superoxide anion. This enzyme could act as a sensor of the concentration of oxygen in the vasculature modulating the vascular tone. Components of the NADPH oxidase were demonstrated in vascular and renal cells in animals and humans.

The ROSs produced in the vascular wall are involved in various cellular events such as mitosis, apoptosis, migration, hypertrophy and extracellular matrix modification, and changes in gene transcription and protein synthesis. They may also function as mediators of the metabolic memory to hyperglycemia. Human retinal endothelial cells exposed to hyperglycemia in vitro, maintained high levels of oxidative stress markers such as PKC and β subunits of NADPH oxidase p47phox, even after normalization of blood glucose levels.

Another important source of ROS in diabetes is the mitochondria. It is postulated that the mitochondrial anion acts as a factor initiating a cascade of events that result in increased production of ROS and reactive nitrogen species (RNS) through activation of NFκ-B. This

results in the production of inflammatory cytokines, activation of PKC and NADPH oxidase. In addition, NOS can divert the production of nitric oxide (NO) to generate in conditions of deficiency of L-arginine or tetrahydropterin in the endothelium of diabetic patients. When both are produced the formation of peroxynitrite (NOO^-) occurs, causing damage to cellular structures such as DNA, lipids, and proteins.

Under normal conditions, the presence of ROS induces the expression of antioxidant enzymes as a defense mechanism. This is not a rule under diabetes condition. For instance, in fibroblasts from T1D patients with overt nephropathy, the exposure to hyperglycemia led to an increase in lipid peroxidation without a compensatory increase in the level of the antioxidant enzyme Cu-Zn superoxide dismutase, catalase, and glutathione peroxidase. Even patients with a short diabetes duration and without chronic complications present less antioxidant plasma capacity and uric acid levels suggesting that the oxidative stress occurs early in the disease.

Nonenzymatic extracellular antioxidants include α-tocopherol, vitamin A, β-carotene, ascorbic acid, albumin, and uric acid. The lipid solubility properties of α-tocopherol, vitamin A, and β-carotene are particularly important to protect against lipid peroxidation. The role of uric acid in the pathogenesis of CVD and endothelial dysfunction is still conflicting. Another important component of the antioxidant defense in diabetes is haptoglobin. This plasma protein binds free hemoglobin resulting in the inhibition of iron-induced oxidative damage, since hemoglobin released in the blood after hemolysis of senescent erythrocytes is a potent oxidant.

Epigenetics:

Nowadays, there is compelling evidence linkingepigenetic factors to many human diseases including diabetes and CVD. Epigenetic factors, by different types of reactions, could mediate the interplay between genes and environment resulting in activation or repression of genetic transcription, or even silencing the genetic transcription. The most important epigenetic reactions affecting genetic transcription are acetylation and methylation. These reactions occur mainly in the tail of histones that are proteins where DNA is wrapped. Brownlee et al. have demonstrated in human aortic endothelial cells that excess ROS resulting from hyperglycemia can induce monomethylating of lysine from histone 3 increasing the expression of the subunit p65 of NF*L*-B. This reaction is responsible for the increased transcription of vascular cell adhesion molecule 1 (VCAM-1), monocyte chemoattractant molecule 1 (MCP-1), and some inflammatory proteins like interleukin 6 (IL-6), intercellular adhesion molecule 1 (ICAM-1), and NOS that are related

to hyperglycemia-induced arterial pathology. Moreover, this reaction persisted after a six-day period of subsequent normoglycemia, supporting the concept of metabolic memory. Epigenetic reactions could be an important mediator between diabetes, CVD, and chronic inflammatory response. Besides, some comorbidities associated with diabetes have also been associated with epigenetics like hypertension andobesity. The epigenetic modifications associated with hypertension are related to intrauterine environmental factors which can limit the development of the nephrons and to other factors that are related to autonomic responsiveness, vessel remodeling, salt sensitivity, and to the renin-angiotensin system. The mechanisms involved in these associations are mainly methylation of histones and of DNA. The relationship between epigenetics and obesity is more complex and is related to genomic imprinting, epigenetic mosaicism, and nonimprinted gene which through different pathways can influence energy balance, body weight, and fat mass.

8. Inflammatory Cascade, Diabetes, and Atherosclerosis:

Diabetes, obesity, and insulin resistance are associated with subclinical inflammation characterized by overexpression of cytokines produced by adipose tissue, activated macrophages, and other cells Inflammatory mediators, such as TNF-α, interleukin-1 (IL-1), IL-6, leptin, resisting, MCP-1, plasminogen activator inhibitor-1 (PAI-1), C-reactive protein (CRP), fibrinogen, angiotensin, vastatin, retinol binding protein-4, and adiponectin are involved in signaling pathways, in insulin action, and perpetuation of inflammatory response . These cytokines are involved in the chronic inflammatory process of the vessels wall, promoting lipid accumulation with consequent development of atherosclerosis and CVD.

Atherosclerosis is a complex multifactorial disease, and the acceleration of atherosclerosis in diabetes may be explained by several conditions including hyperglycemia, increased oxidative stress, advanced glycation end products (AGE), dyslipidemia, autonomic imbalance, hyperinsulinemia, inflammatory markers excess, and genetic variables.

It is assumed that the adipose tissue initiates obesity-induced inflammation and leads to the recruitment of immune cells which contributes to the maintenance of inflammatory response, besides leading to endothelial dysfunction with increased expression of adhesion molecules (ICAM-1, VCAM-1, P-selectin, and E-selectin), migration of monocytes, neutrophils, and T lymphocytes.

Insulin resistance induces chronic elevation in FFA plasma concentrations leading to increased storage of triglycerides in muscle, promoting reduction of muscle glucose uptake and liver, and increased hepatic glucose production, that have been shown to impair insulin action and promote hyperinsulinemia. Hyperinsulinemia can, per se, induce cardiomyocyte hypertrophy through myocyte growth induced by an activation of PI3 K/Akt-1 pathway and also by enhancing FFA levels. FFA are also implicated in the development of myocardial contractile dysfunction.

Several cytokines described to be related with insulin resistance are also involved with the development of atherosclerosis and CVD. TNF-α and other cytokines, FFA and ROS, activate inflammatory pathways and promote the expression of numerous genes involved in insulin resistance.

IL-1 is another cytokine produced as a consequence of stress or cell injury mainly by macrophages that modulate key events in the process of atherosclerosis such as vessels wall inflammation, leukocyte chemotaxis and adhesion by increasing expression of VCAM-1 and MCP-1, angiogenesis (through vascular endothelial growth factor—(VEFG) induction), upregulation of matrix metalloproteinases (MMP), and destabilization of atheromatous plaques, that can lead to plaque rupture and thrombosis.

CRP is an acute phase protein and is primarily derived from IL-6 hepatic biosynthesis. Atherogenic mechanisms of CRP include impaired production of endothelial NO and prostacyclin; increased production of endothelin-1 and other cell adhesion molecules, monocyte chemoattractant protein-1, IL-8, and PAI-1; ROS and proinflammatory macrophage production; monocyte adhesion and chemotaxis; uptake of oxidized low-density lipoprotein (LDL); CRP also stimulates the expression of metalloproteinases, activates NF-*d*B, and promotes cell proliferation in vascular smooth muscle cells due to upregulation of the angiotensin type 1 receptor .

Adiponectin has many protective actions in the atherosclerosis process due to its inhibition of LDL oxidation, activation of macrophages (via TNF-α), reduction of adhesion molecule (VCAM and ICAM), inhibition of proliferation and migration, of smooth cells, and an increased production of NO in endothelial cells. Adiponectin is markedly reduced with increased obesity, and in diabetes and hypoadiponectinemia is associated with an increase in CVD rates.

Leptin is a hormone secreted by adipose tissue and primarily involved in the regulation of energy expenditure and food intake. Plasma leptin concentrations are increased in obese and diabetic patients. Leptin has been shown to participate in the development of atherosclerosis in several

ways: inducing oxidative stress; increasing the production of MCP-1, endotelin-1 (ET-1) which leads to cardiomyocyte hypertrophy; promoting migration, proliferation, hypertrophy of vascular smooth muscle cells (VSMC), and vascular cell wall calcification; stimulating platelet aggregation; attenuating cardiomyocyte contractility through increased nitric oxide production, reduction of intracellular calcium, and decreased β-adrenergic response .

Therefore, evidence suggest that the hypothesis that is low-grade inflammation would be the causal common factor between diabetes, insulin resistance, obesity, and CVD.

Endothelial Dysfunction:

Endothelial vasodilation and vascular reactivity in diabetes are known to be impaired since its early phases. This is explained by the hypothesis that there are changes in endothelial cells function present in the early atherosclerosis lesion. Thus, oxidative stress, inflammation, and endothelial dysfunction are closely correlated in diabetes, because the formers increase vascular endothelial permeability, generating leukocyte adhesion, which is coupled with impairment in endothelial signal transduction and redox-regulated transcription factors. Another possible mechanism to link these conditions is that the impaired endothelium-dependent vasodilation in diabetes is associated with reduced action of NO secondary to its inactivation, and this is a consequence of oxidative stress, rather than decreased NO production from endothelial cells. Moreover, the abnormal metabolism of NO is related to advanced diabetes microvascular complications. Many factors can explain endothelial dysfunction in diabetes such as hyperlipidemia, insulin resistance,hyperglycemia,hyperamylasemia,hypertension, and hyperhomocysteinemia .

Endothelial Dysfunction in T1D:

Endothelial function of the macro- and microcirculation, which is usually evaluated through the vasodilator response to endothelium-dependent vasodilators or physiological stimuli, is characteristically impaired in patients with T1D. The endothelial response to acetylcholine is correlated with diabetes duration, glycemic control, triglycerides, and age.

Endothelial dysfunction in T1D is an important determinant of inflammatory activity regardless of the presence or absence of complications showing that it can be considered an early marker for CVD. The disturbances in vascular responses can be seen even in children with T1D, as evidenced in studies that showed impaired flow-mediated dilation (FMD) responses

andassociation with increased carotid artery intima-media thickness in this group. And, as evidenced by Davi et al., this alteration represents an early and, in some cases, a reversible event in the natural history of T1D in children and adolescents because it was noted that in approximately 45% of this population the tissue plasminogen activator (tPA) levels were reversed after 1 year.

Several markers of endothelial function in T1D have been described such as Von Willebrand factor, thrombomodulin, selectin, PAI-1, Type IV collagen, and tPA, that are so forth indicators of endothelial cell dysfunction when increased. VCAM-1 levels are more markedly increased in patients with T1D with retinopathy when compared with those with micro- or macroalbuminuria only. It has been shown that the cellular adhesion molecule E-selectin may enhance CAD prediction beyond traditional risk factors in T1D. Other markers of low-grade inflammation levels are described to be elevated in this group such as of oxidized LDL, monocyte IL-6, superoxide anion, plasma CRP, sCD40L, and nitro tyrosinelevels.

So, endothelial dysfunction in T1D represents a high risk for micro- and macroangiopathy and hyperglycemia, appears to be one of the main causes, that alone seems not to be sufficient to cause it, because other agents such as genes and environmental factors are likely to play a role.

Endothelial Dysfunction in T2D:

T2D is independently associated with impaired FMD, and endothelial dysfunction is the determinant factor for the vascular complications that is aggravated, rather than caused by hyperglycemia, because of the presence of many other risk factors such as obesity, hypertension, dyslipidemia, and ageing as well. One possible explanation for this is the increased calpain (calcium-dependent protease) activity in response to hyperglycemia. Hyperglycemic states can induce loss of NO via a calpain-dependent decrease in the association with endothelial NOS. Moreover, inhibition of calpain activity decreases endothelial cell surface expression of the proinflammatory adhesion molecules ICAM-1 and VCAM-1 during hyperglycemia. Markers of endothelial dysfunction are early signs for the development of microangiopathy.

The hallmark of T2D is insulin resistance, therefore there is sufficient evidence pointing to the coexistence of endothelial dysfunction with this condition. Elevated circulating levels of PAI-1 and ET-1 can be seen in obesity as well as the correlation between endothelial activation and acute-phase reaction with insulin resistance and obesity in T2D. Abnormalities in vascular

reactivity and insulin resistance can also be seen in young first-degree relatives of T2D patients independent of the presence of classic cardiovascular risk factors.

Cardiovascular Autonomic Neuropathy (CAN):

CAN is one of the most common chronic complications of diabetes mellitus and has shown negative impact on survival and quality of life in patients with diabetes. The prevalence of CAN ranges from 2.6% to 90% among subjects with diabetes, and the incidence of CAN increases with age, diabetes duration, and inadequate glycemic control.

Recent studies have shown that dysregulation of the Autonomic Nervous System (ANS) with increased sympathetic activity is associated with elevated inflammatory markers such as IL-6 and CRP, demonstrating a link between autonomic imbalance, inflammation, and CVD. The ANS is responsible for modulating the activity of the sinus node (heart rate), ventricular (end systolic and diastolic volume) and blood vessels (systemic vascular resistance), and the dysfunction of the ANS may contribute to the development of arterial stiffness, left ventricular hypertrophy, and ventricular diastolic dysfunction.

The clinical manifestations of CAN are described as resting tachycardia, postural hypotension, exercise intolerance, abnormal coronary vasomotor regulation (risk of silent myocardial ischemia and infarction), increased QT interval, perioperative instability, increased risk of renal disease, stroke, and sudden death.

CAN represents a strong indicator of cardiovascular risk in both T1D and T2D. In the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects (DIAD) study, the strongest predictors for abnormal perfusion tests were abnormal Valsalva maneuver, male sex, and diabetes duration, demonstrating that CAN may have an important role in the screening of CVD. Patients with diabetes and CAN have 5-year mortality rates ranging from 16 to 53%, depending on its severity. The mortality rates from CVD in T1D and T2D are 4.2 and 10 times higher, respectively, than in healthy individuals without diabetes.

Screening for Subclinical Atherosclerosis:

The screening for the detection of subclinical atherosclerosis in asymptomatic diabetic patients is the subject of considerable controversy. There are no prospective studies that support its usefulness and that can modify the natural history of those patients. Even today, there is no consensus on which tests should be performed. Intensive medical therapy seems to provide equal outcomes to invasive revascularization. Which raises questions on how screening results would change management? The clinical risk factors that indicate increased risk of CVD in diabetic patients are CAD, cerebrovascular or peripheral vascular disease, female sex, age greater than 40 years in men and greater than 50 years in women, long duration of diabetes (for every 10 years the risk increases 86% according to the Framingham study), presence of renal disease, autonomic neuropathy and classic risk factors such as hypertension, dyslipidemia, smoking, sedentary lifestyle, family early atherosclerotic disease, metabolic syndrome, and presence of atrial fibrillation .

One of the major limitations of the routine screening for subclinical atherosclerosis is the different rates of coronary events in previous studies. The prevalence of silent myocardial ischemia (SMI) in diabetic population varies in different studies, ranging from 12% to almost 57% . This variability underlines the difficulty to have a cost-effective screening and the necessity to define the cardiovascular risk in the asymptomatic diabetic population who could benefit from this screening. The ADA does not recommend the detection of CVD in asymptomatic diabetic patients as a routine. Their recommendations for investigating SMI are very conservative, being the exercise testing in diabetic patients with typical (chest pain, dyspnea) or atypical cardiac symptoms and changes in baseline electrocardiogram. Asymptomatic patients with carotid or peripheral vascular disease or sedentary patients who want to start high-intensity exercise can also be investigated. The DIAD study accessed 1,123 asymptomatic diabetic patients in a randomized controlled trial. The patients were randomly assigned to be screened with adenosine-stress radionuclide myocardial perfusion imaging (MPI) or not to be screened. The cumulative cardiac event rate was 2.9% over a mean (SD) followup of 4.8 years for an average rate of 0.6% per year. A comparison of the cardiac event rates (0.6% per year) with those reported in ACCORD trial for the subgroup of patients with T2D without previous cardiac events (1.4% per year) which included a selection of older patients with specific

additional risk factors for CVD would appear favorable and compatible in these two studies. The data from these two studies show that there is no evidence that the complete survey of subclinical arterial disease may modify the natural history of CAD in asymptomatic diabetic patients with risk factors controlled by recommended goals.

Despite the controversy regarding the screening, several studies using various invasive and noninvasive cardiovascular examinations are being conducted. The presence of calcium in coronary arteries is a specific marker of atherosclerosis, independent of its etiology. The presence of calcified plaques correlates with increasing age, especially after age 50. Though the calcium score represents an estimate of the total amount of plaque present in an individual, it does not correspond directly to the degree of luminal narrowing of a given vessel. The calcium score was higher than the scores of Framingham and UKPDS for the prediction of events. According to the Patients with Renal Impairment and Diabetes undergoing Computed Tomography (PREDICT) study, the coronary artery calcium (CAC) score was taken as independent risk marker for incremental coronary events and stroke.

The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) recommends the use of calcium score in a selection of patients with intermediate risk by traditional methods (between 10 and 20% risk in 10 years), and when added to conventional methods, these patients may become high risk, and benefit of a therapy aimed to more restrictive treatment targets. A recently meta-analysis showed that diabetic patients without a history of myocardial infarction had 43% less risk of developing coronary events when compared with patients without diabetes but with prior infarction. Both coronary calcifications as average intimal thickness are increased in this population; however, the classification of these individuals to a higher category of risk is still controversial when using these methods. Although being very promising the use of the calcium score for CVD in asymptomatic diabetic patients still needs further prospective studies and cost effectiveness to demonstrate its benefits.

Revascularization of asymptomatic T2D subjects is still polemic. The Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial (BARI 2D) was a randomized study with 2,368 patients with T2D and SMI comparing revascularization versus intensive medical therapy, showed no differences on reducing rates of death and cardiovascular events among patients undergoing prompt revascularization and those undergoing medical therapy or between strategies insulin sensitizers or insulin provision.

According to the 2010 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults, in asymptomatic adults with diabetes, 40 years and older, measurement of CAC score is reasonable for cardiovascular risk assessment (Class Il, evidence B). Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or when previous risk assessment testing suggests a high risk of CHD, such as CAC score of 400 or greater (Class IIb, evidence C).

Carotid intima-media thickness (C-IMT) is considered one of the independent predictors of coronary artery disease, a marker of early atherosclerosis and vascular remodeling. According to Ire et al. in an evaluation of 251 asymptomatic T2D patients, the addition of max-IMT (the greatest IMT in the observation-possible areas) to conventional risk factors improves the risk stratification for CAD [133]. In T1D patients, the DCCT/EDIC research group demonstrated that in 12 years after the DCCT intervention the C-IMT progression in the group that received intensive diabetes therapy was slower than the group that received conventional therapy from years 1 to 6. It could be assigned to a durable "metabolic memory" that exists for atherosclerosis. But, the similar C-IMT progression in the original treatment groups over EDIC from years 6 to 12 indicates a "metabolic memory amnesia" over time.

The ankle brachial pressure index (ABPI) is a simple method to evaluate the presence of peripheral vascular diseases. A low ABPI (<0.9) was considered to be a marker of cardiovascular diseases risk. The AHA recommends the evaluation of ABPI as a diagnostic criterion for the prevalence of peripheral arterial diseases [136]. In the study of Doza et al. with 1,121 T2D patients in north India, the prevalence of low ABPI was 4.5% in men and 4.7% in woman. The results were similar to those found in studies with Chinese Korean and Brazilian populations.

Changing the natural history of silent coronary artery disease, without considering the control of classical risk factors, represents a major challenge facing the global epidemic of diabetes mellitus. More research is needed to identify appropriate screening strategies for diabetic asymptomatic patients with CHD.

Perspectives and Conclusions:

The incidence of diabetes is sharply increasing worldwide which represents an important burden for patients and for the society as well due to micro- and macrovascular complications that

people with this condition may experience and consequently cardiovascular diseases that are the most prevalent causes of morbidity and mortality among patients with diabetes.

The classical risk factors for the development of CVD in subjects with diabetes are the presence of poor glycemic control, obesity, dyslipidemia, and hypertension. In recent decades, several clinical trials have investigated the effect of intensive treatment of hyperglycemia on cardiovascular risk reduction, in both T1D and T2D, like the DCCT and UKPDS, and the main lesson learned from these trials is that intensive treatment of hyperglycemia initiated early in patients with short duration of diabetes and low cardiovascular risk, result in cardiovascular benefits. The same is not true for older patients exposed to hyperglycemia for a long time and with a high cardiovascular risk profile. This protection might result from a mechanism known as "metabolic memory," which means that the effect of the early glycemic exposure environment is imprinted in target organs resulting in long-term deleterious or protective effects. Obesity, especially with visceral fat deposition, is associated with low-grade inflammation, which plays a role in the pathogenesis of diabetes, and both diseases are associated with significant increase in morbidity and mortality due to CVD. Dyslipidemia mainly that represented by high levels of LDL-cholesterol is also a risk factor for CVD because small increases in LDL-cholesterol levels increase the risk for CVD. The coexistence of hypertension and diabetes increase the risk of developing macrovascular complications (myocardial infarction, stroke) and also microvascular complications (nephropathy and retinopathy).

These clinical conditions might be associated with intracellular and mitochondrial metabolic changes that can result in oxidative stress, a state of low-grade inflammation characterized by overexpression of cytokines produced by adipose tissue, activated macrophages and other cells, and the presence of many inflammatory mediators that will finally cause a generalized endothelial dysfunction or even a cardiovascular autonomic neuropathy, an important cause of sudden death among subjects with diabetes.

The proposed mechanisms that can link accelerated atherosclerosis and increased cardiovascular risk in subjects with diabetes are still poorly understood. It has been suggested that an association between hyperglycemia and epigenetic factors by different types of reactions could be responsible for the interaction between genes and environment and for this reason account for the association between diabetes and cardiovascular disease. Many trials have shown that an early intervention in patients with short duration of diabetes could result in cardiovascular benefits, but

there is no robust evidence that justify screening for subclinical atherosclerosis in asymptomatic patients with diabetes.

The purpose of this paper was to describe the association between poor glycemic control, oxidative stress, markers of insulin resistance and of low-grade inflammation that have been suggested as putative factors linking diabetes, and cardiovascular disease and to elucidate the mechanisms involved in the pathogenesis of CVD in this population. (8)

1.5 Global estimates for the prevalence of diabetes for 2015 and 2040:

1.5.1 Introduction:

Diabetes mellitus is a term used to describe a collection of metabolic illnesses characterized by high blood glucose levels. Diabetes patients have a greater morbidity and mortality rate than the general population. Among recent decades, the global prevalence of diabetes in adults has risen. Diabetes was projected to affect 30 million people in 1964. The WHO predicted that 171 million people worldwide had diabetes less than 40 years later. Global diabetes prevalence was projected to be 151 million in 2000, 194 million in 2003, 246 million in 2006 , 285 million in 2009 , 366 million in 2011 , and 382 million in 2013 by the International Diabetes Federation (IDF). Each estimate was made using the most recent information available.

Diabetes has increased dramatically in all countries, and in both rural and urban areas. Diabetes prevalence estimates and predictions at the global, regional, and country levels are needed to plan and evaluate prevention and treatment efforts, as well as to assess progress toward the Global Action Plan for Noncommunicable Diseases and the Sustainable Development Goals.

1.5.2 Materials and Method:

Study selection:

A non-restricted search of PubMed, Medline, and Google Scholar was done to discover data sources giving age-specific prevalence of diabetes from studies conducted between January 1990 and June 2015. ("diabetes" OR "impaired glucose tolerance") AND "prevalence" AND ("country name" OR "region/continent"); "cardiovascular risk factors" AND ("country name" OR "region/continent") were used as search terms. Furthermore, data was acquired via national health surveys undertaken by governments or international organizations such as the World Health Organization (WHO). Relevant citations from published literature were also examined, and IDF network investigators were engaged to locate additional data sources.

The studies' methodological information was gathered. The studies were then categorized using the following criteria: sample size; study type (e.g., population-based, clinic-based, diabetes registry, medical records review); representation (e.g., nationally representative, regionally representative, single city or village, single ethnic group or cohort); year of the survey; and kind of publication (e.g., peer-reviewed publication, national health survey, Stepwise approach to Surveillance study, personal communication).

Studies were excluded if they lacked sufficient methodological information for characterization, did not provide enough data on age-specific diabetes prevalence, were conducted in hospital or clinic-based settings, were based solely on pharmacologically treated diabetes, or were conducted prior to 1990. Studies that solely reported the prevalence of type 1 diabetes, newly diagnosed diabetes, or had contradictory results were also removed.

The R statistical tool, version 3.1.0, was used for the analyses. Diabetes prevalence by age and gender was calculated for each country in urban and rural settings. After data was retrieved, logistic regression was used to create smoothed sex- and age-specific prevalence estimates for adults aged 20–79 years. If available, the regression employed age (as the midpoint of each age-group) and the quadratic of age as independent variables for each sub-group (sex- and urban/rural setting-related). The quadratic element was added to allow for a reduction in diabetes prevalence among the oldest age groups. When the sample size in a single group was less than 50 for some sources, point adjustments were made by mixing age groups to reduce variability.

Where primary data were not stratified by urban/rural status, a ratio was used to estimate the proportion of diabetes in each setting, which was derived from aggregated data available within one IDF region and the percentage urbanization by country available from the UN Population Division Urbanization Prospects. The urban-to-rural ratio was 1.0 in high-income counties.

Undiagnosed diabetes cases and estimated ratios of undiagnosed cases to total number of cases were also obtained from the data source, where such information was available. This estimation strategy also included a data source selection step in which appropriate studies were selected utilizing the analytic hierarchy methodology, as explained above.

Diabetes health expenditure estimates:

Using previously described technique, estimates of total diabetes health expenditures and mean diabetes health expenditures per person were estimated in both US Dollars (USD) and

International Dollars (ID). This strategy assumes that the average health expenditure for those with diabetes is twice that of people without diabetes.

Diabetes mortality estimates:

Diabetes-related deaths were also updated for each UN-ratified country. The methods used to generate these estimations have already been detailed, To summarize, the number of deaths attributed to diabetes was calculated using the following inputs: WHO life tables for the estimated number of deaths in 2010; country-specific diabetes prevalence by age and sex for the year 2015; age- and sex-specific relative risks of mortality for diabetics compared to those without diabetes These inputs were used to model the estimates using Dismoded II, a tool developed for the Global Burden of Disease study in 2000, and the number of fatalities attributable to diabetes in people aged 20–79 years was calculated using Miettinen's formula for the population-attributable percentage.

1.5.3 Results:

Study selection: The analytic hierarchy process ranked the most important study characteristics as (1) sample representation (nationally representative scoring most highly, followed by regionally representative), (2) diagnostic criteria (oral glucose tolerance test scoring most highly), (3) sample size (5000 people or more scoring most highly), and (4) age of study (less than 5 years old scoring most highly)

The literature search identified 540 data sources from 154 countries. Of these, 196 data sources were selected based on the analytic hierarchy process, representing 111 countries. Most data sources (178 out of 196) were nationally representative. All studies in the selected list were population-based, although only 62 used the oral glucose tolerance test as a method of diagnosis.

The South-East Asia Region had original data sources from the highest proportion of countries (86%) within the region. Original data sources were available from 76% of countries in the Middle East and North Africa Region, 62% in the Western Pacific Region, 59% of countries in the Europe Region, 45% in the South and Central America Region, and 39% in the North America and Caribbean Region. The Africa Region had the lowest proportion of countries with original data sources, at only 24%.

Although there was an increase in the number of data sources providing information of diabetes prevalence, and with 144 out of 173 studies being nationally-representative, there remained a shortage of high-quality studies in 95 countries around the world. For example, in the Africa

Region and the North America and Caribbean Region, less than half of countries were represented by original data. Even though 59% of countries in the Europe Region were represented by population-based studies, only 14% of countries had studies that used oral glucose tolerance tests.

Prevalence estimates of diabetes, impaired glucose tolerance, and hyperglycemia in pregnancy: These data sources were used to produce an estimate of 415 million cases (uncertainty interval: 340–536 million) of diabetes among adults aged 20–79 years in 220 countries and territories for 2015. For 2040, it was estimated that 642 million (uncertainty interval: 521–829 million) people aged 20–79 will have diabetes

Table 1.1: Prevalence estimates of diabetes

Empty Cell	2015	2040
General population		
Total world population	7.3 billion	9.0 billion
Adult population (20–79 years)	4.7 billion	6.2 billion
Total live births to women aged 20–49 years	129.4 million	NC
Diabetes (20–79 years)		
Global prevalence (uncertainty interval)	8.8% (7.2–11.4%)	10.4% (8.5–13.5%)
Number of people with diabetes (uncertainty interval)	415 million (340–536 million)	642 million (521–829 million)
Number of deaths due to diabetes	5.0 million	NC
Health expenditure due to diabetes (20–79 years)		
Total health expenditure, 2015 USD	673 billion	802 billion
Impaired glucose tolerance (20–79 years)		
Global prevalence (uncertainty interval)	6.7% (4.5–12.1%)	7.8% (5.2–13.9%)
Number of people with impaired glucose tolerance	318 million (212–572 million)	481 million (317–856 million)
Hyperglycemia in pregnancy (20–49 years)		
Global prevalence	16.2% of live births	NC
Number of live births affected	20.9 million	NC
Proportion of hyperglycemia in pregnancy cases due to gestational diabetes	85.1%	NC

The global diabetes prevalence in adults aged 20–79 years was estimated at 8.8% (uncertainty interval: 7.2–11.3%). There were differences in the prevalence of

diabetes by age group, World Bank income group, and geographical region. Diabetes prevalence was higher in high- and middle- income countries compared to low-income countries (Fig. 1a). Three quarters (75%) of people with diabetes were estimated to be living in low- and middle-income countries (data not shown). Diabetes prevalence peaked at ages 65–69 years for men and ages 75–79 years for women (Fig. 1b). The prevalence in people aged 80 years and over was not calculated. The highest world-standardized diabetes prevalence was in the North American and Caribbean Region (11.5%, uncertainty interval: 9.5–13.0%). The lowest world-standardized prevalence of diabetes in adults was in the Africa Region (3.8%, uncertainty interval: 2.6–7.9%) (Fig. 1c). The largest number of people with diabetes (153.2 million, uncertainty interval: 135.3–187.7 million) was found in the Western Pacific Region. Over half (56%) of all people with diabetes were living in the South-East Asia Region or the Western Pacific Region in 2015 (Fig. 1d). The regions that are projected to experience the highest growth rates in the number of people with diabetes are the Africa Region (140.7% increase by 2040) and the Middle East and North Africa Region (103.8% increase by 2040) (Fig. 1d).

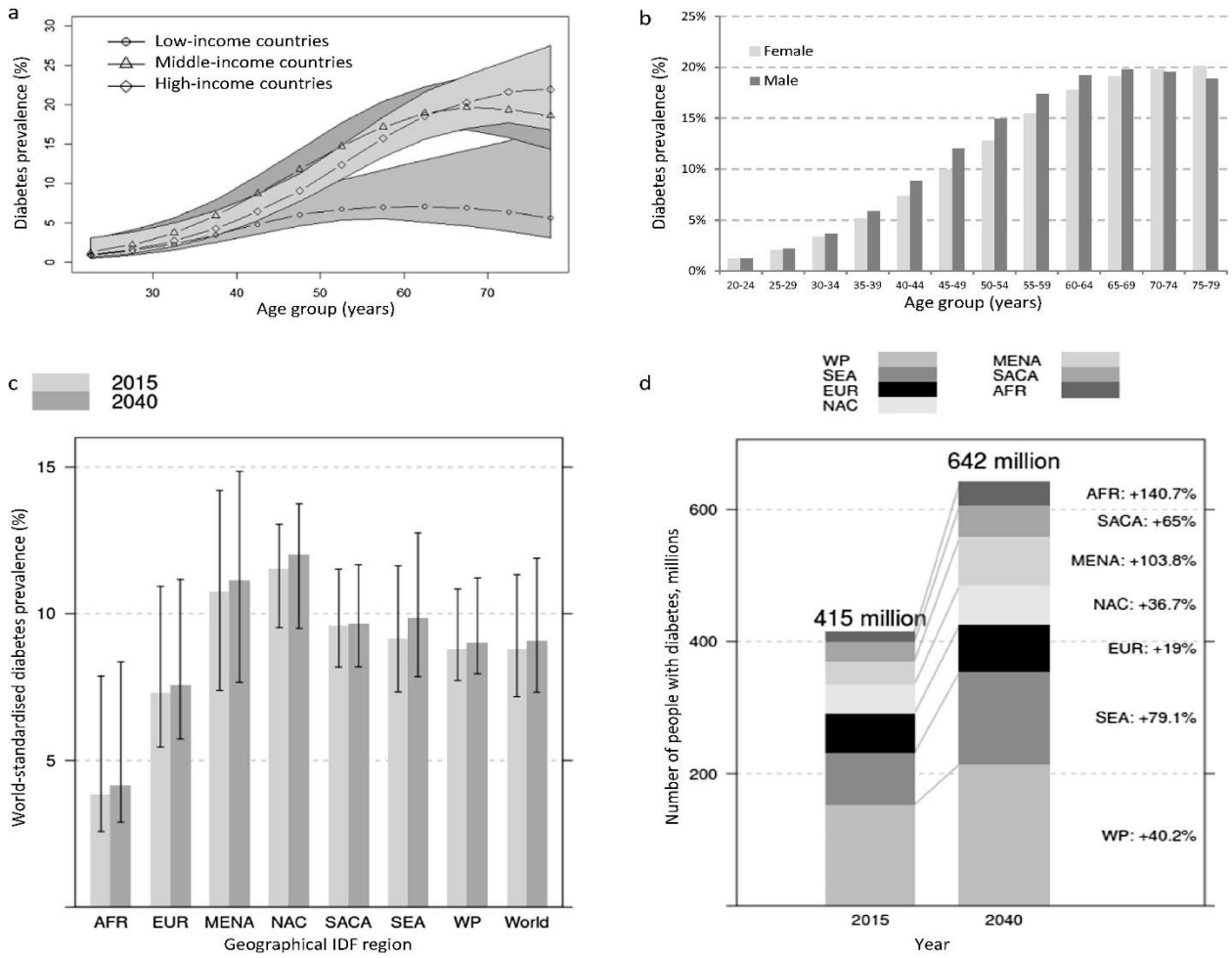

Fig. 1.2. Global and regional diabetes prevalence estimates for adults

Aged of 20–79 yearswhere (a) Prevalence of diabetes by age group and World Bank income group for 2015, (b) global prevalence of adults with diabetes by age group and sex for 2015, (c) world-standardised prevalence of diabetes by IDF region for 2015 and 2040, (d) total number of adults with diabetes by IDF region for 2015 and 2040. IDF = International Diabetes Federation, AFR = Africa, EUR = Europe, MENA = Middle East and North Africa, NAC = North America and Caribbean, SACA = South and Central America, SEA = South-East Asia, WP = Western Pacific.

Only half of all data sources (94 out of 196) reported undiagnosed diabetes. Using these data, and extrapolating to the countries not reporting undiagnosed diabetes, it is estimated that, globally, 46.5% of adults aged 20–79 years with diabetes were undiagnosed in 2015 (Table 2). The Africa region had the highest percentage of undiagnosed diabetes, at an estimated 66.7% of all cases of diabetes in the region. It was also estimated that over 50% of adults with diabetes in

the South East Asia and Western Pacific Regions were undiagnosed (Table 2). The lowest estimated proportion of people with undiagnosed diabetes was in the North America and Caribbean Region (21.4%), however this estimate was based largely on estimates from Canada and the USA. Estimates from Belize, Haiti, Mexico, USA, and the US Virgin Islands were derived from studies using oral glucose tolerance tests. There were very few data sources on the proportion of people with undiagnosed diabetes in the Caribbear

Table 1.2: Global and regional estimates of the proportion and number of adults (20–79 years)

IDF Region	Proportion of adults (20–79 years) with diabetes who are undiagnosed (%)	Number of adults (20–79 years) with undiagnosed diabetes (million)
Africa	66.7	9.5
Europe	39.3	23.5
Middle East and North Africa	40.6	14.4
North America and Caribbean	29.9	13.3
South and Central America	39.0	11.5
South-East Asia	52.1	40.8
Western Pacific	52.1	79.8

IDF Region	Proportion of adults (20–79 years) with diabetes who are undiagnosed (%)	Number of adults (20–79 years) with undiagnosed diabetes (million)
World	46.5	192.8

Diabetes health expenditure estimates: Total global health expenditure due to diabetes was estimated at 673 billion US dollars for 2015 and 802 billion US dollars for 2040. Approximately 12% of global health expenditure was estimated to be dedicated to diabetes, and the mean health expenditure per person with diabetes was 1917 International Dollars. The highest proportion of health dollars spent on diabetes was in middle-income countries (12.5%), while the lowest proportion was spent in low-income countries (5.9%). The proportion of health expenditure spent on diabetes in high-income countries was 11.4% (Fig. 2a). Men aged 60–69 years were the population group responsible for the largest spending on diabetes (102 billion US dollars) (Fig. 2b). In terms of IDF regions, the Middle East and North Africa Region spent the highest proportion of health expenditure on diabetes (15.2%), while the Africa Region spent the lowest proportion (7.0%) (Fig. 2c). While the number of people with diabetes is expected to grow by 54.7% between 2015 and 2040, the global health expenditure on diabetes is only expected to increase by 25.4% (Fig. 2d), because a large proportion of total health expenditure occurs in high-income countries, but most of the growth in diabetes is projected to occur in low- and middle-income countries.

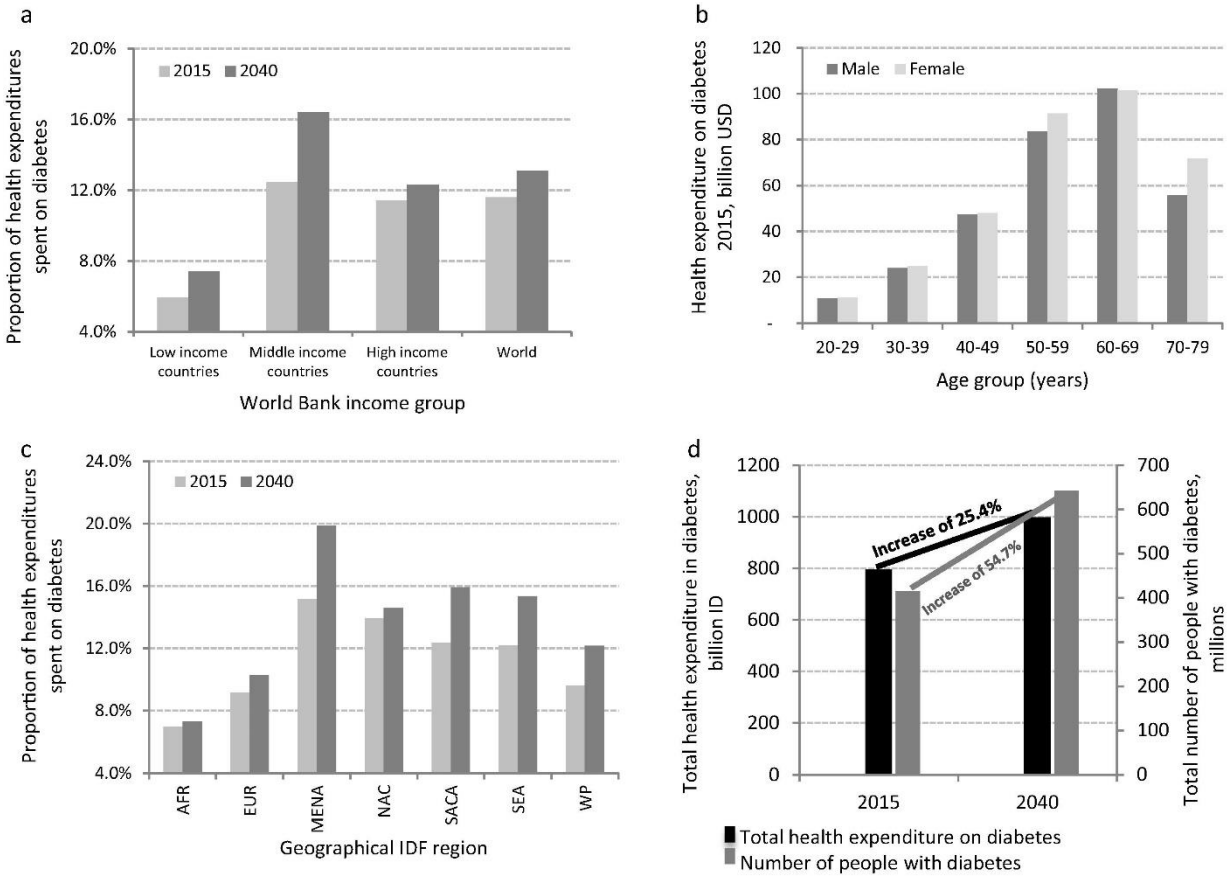

Fig. 1.3.: Global and regional diabetes health expenditure estimates for adults

Agedof 20–79 years,where R = 2*. (a) Proportion of total expenditure on health spent on diabetes globally and in low-, middle-, and high-income countries for 2015 and 2040, (b) health expenditures on diabetes by age-group and sex in ID for 2015, (c) percentage of total expenditure on health spent on diabetes by region for 2015 and 2040, (d) global health spending on diabetes (ID) vs diabetes cases. *The R = 2 estimates assume that health expenditures for people with diabetes are, on average, 2-fold higher than people without diabetes. ID = International Dollars, IDF = International Diabetes Federation, AFR = Africa, EUR = Europe, MENA = Middle East and North Africa, NAC = North America and Caribbean, SACA = South and Central America, SEA = South-East Asia, WP = Western Pacific.

Diabetes mortality estimates:

In 2015, it was estimated that there were 5.0 million deaths attributable to diabetes in people aged 20–79 years. Diabetes accounted for 12.8% of global all-cause mortality among people aged 20–79 (data not shown). Over 4 million diabetes-attributable deaths in people aged 20–79 occurred in low- and middle-income countries (Fig. 3a). The population group with the highest proportion of deaths from diabetes was women aged 50–59 years, accounting for 20% of all-cause mortality in that group (Fig. 3b). The region with the highest proportion of deaths from diabetes was the Western Pacific Region, accounting for approximately 16% of all-cause mortality in the region (Fig. 3c). Three quarters (75.5%) of all diabetes deaths occurred in people aged 69 years and under (Fig. 3d). In low-income countries, 72.7% of diabetes deaths were in people under the age of 60, whereas this proportion in high-income countries was 29.6%.

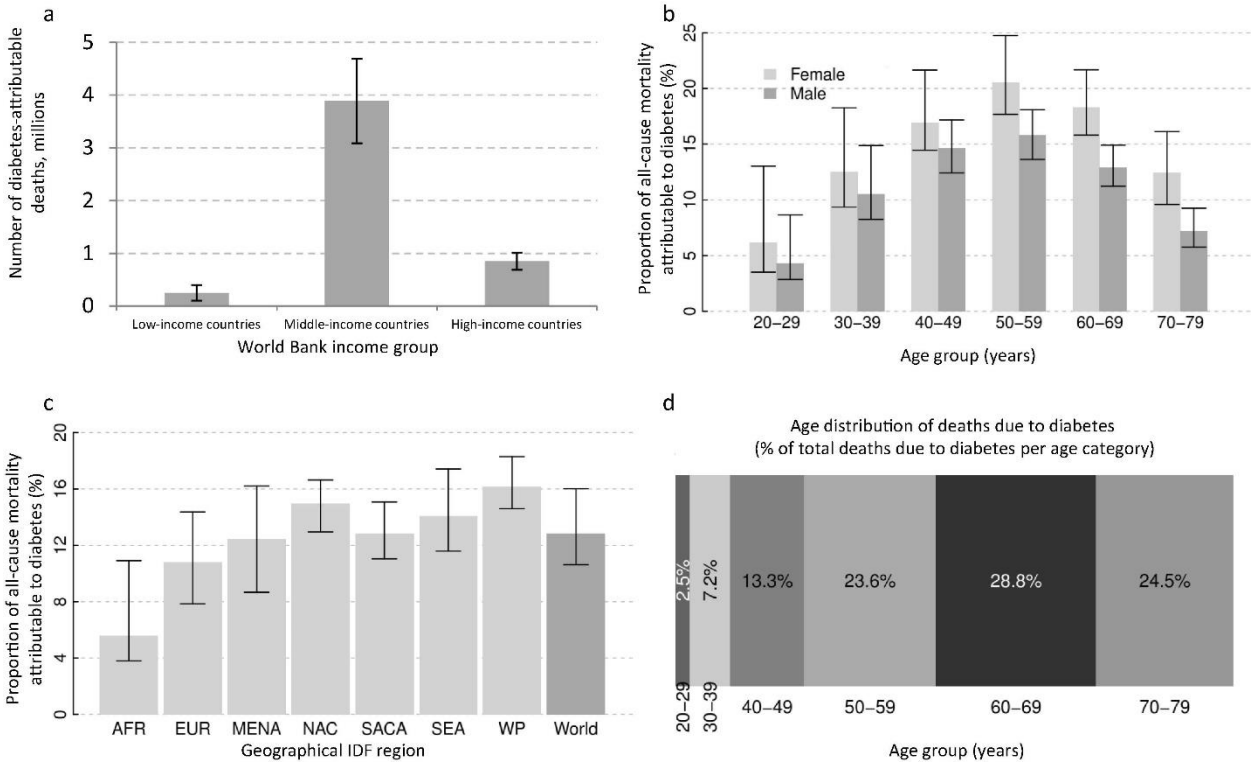

Fig. 1.4.: Global and regional diabetes mortality estimates for adults

Aged of 20–79 years, where 2015. (a) Number of diabetes-attributable deaths in high-, low- and middle-income countries, (b) percentage of all-cause mortality attributable to diabetes by age-group and sex, (c) proportion of all-cause mortality attributable to diabetes by IDF region, (d) age distribution of deaths due to diabetes, as a proportion of total deaths due to diabetes per age category. IDF = International Diabetes Federation, AFR = Africa, EUR = Europe, MENA = Middle East and North Africa, NAC = North America and Caribbean, SACA = South and Central America, SEA = South-East Asia, WP = Western Pacific.

1.5.4 Discussion:

A systematic literature review identified 540 studies on the prevalence of diabetes conducted between the period of 1990 and 2015. Using an analytic hierarchy process, 196 sources from 111 countries were selected. Using extrapolation, logistic regression, and UN population estimates, it was estimated that in 2015 there were 415 million (uncertainty interval: 340–536 million) people with diabetes aged 20–79 years, 5.0 million deaths attributable to diabetes, and a total global health expenditure due to diabetes of 673 billion US dollars. The number of people with diabetes aged 20–79 years was predicted to rise to 642 million (uncertainty interval: 521–829 million) by 2040.

Prevalence estimates of diabetes, impaired glucose tolerance, and hyperglycemia in pregnancy

The 2040 projections may be considered conservative because they do not account for the changes in global obesity rates or other diabetes risk factors. There are many population-level diabetes risk factors that were not incorporated into the model, such as ethnicity , overweight , highest level of household education , household income , food security , sugar availability , percent of total energy intake from sugars and sweeteners , impaired glucose tolerance , gestational diabetes , and other non-communicable diseases . Changes in any of these risk factors over the next 25 years will influence the accuracy of the 2040 projections.

It was not possible to estimate the number of adults with prediabetes separately, as most of the studies used did not report these groups independently. In high-income countries, a few studies have estimated that approximately 87–91% of all people with diabetes have prediabetes, 7–12% have type 1 diabetes, and 1–3% have other types of diabetes. The relative proportions of type 1 and prediabetes have not been reported in sufficient detail in low- and middle-income countries.

Uncertainty intervals were estimated using a mixed method by combining the raw data uncertainty and the model's sensitivity to data source selection. The 95% uncertainty interval around the "true" global prevalence of diabetes was estimated at between 7.2% and 11.4% of the adult population (age range 20–79 years). Within this interval lies the diabetes prevalence estimate of 8.5% (age range 18–100+), produced by the WHO in 2016 . However, by using only this "one-at-a-time" sensitivity to estimate uncertainty, the approach did not take into account any other potential sources of uncertainty. Other researchers have produced credible intervals using 2.5% and 97.5% percentiles of the posterior distributions of diabetes prevalence produced from a Bayesian model (NCD Risk Factor Collaboration (NCD-Ric) .

The large proportion of people with undiagnosed diabetes means that there are many people worldwide living with high blood glucose, which puts them at high risk of complications such as diabetic retinopathy and cardiovascular disease. Screening high-risk populations for diabetes will help identify those currently undiagnosed, enabling treatment to be initiated to reduce the risk of further morbidity. Several regionally validated risk assessment tools for prediabetes have been developed for this purpose.

Such tools can also help identify those with impaired glucose tolerance. People with impaired glucose tolerance are at increased risk of diabetes, kidney disease, cardiovascular disease, and all- cause mortality . In some populations, lifestyle interventions to prevent or delay progression to prediabetes may be a cost-effective strategy to decrease the risk of mortality and morbidity in

people with impaired glucose tolerance. Gestational diabetes is also a risk factor in both the mother and child for later development of prediabetes and is thus a potent trans-generational driver of increased incidence of diabetes.

Diabetes health expenditure estimates.

The major driver of diabetes costs is the treatment of the related complications. In the USA, hospital inpatient care was responsible for 43% of the total medical cost, and medication to treat complications accounted for 18% of the total medical cost of diabetes . In the United Kingdom, it was estimated that 80% of total diabetes costs were spent on treating complications. Investing in intensive blood glucose control could help to reduce the cost of diabetes complications by up to 32% . Furthermore, in the United Kingdom alone it was estimated that improved diabetes management could lead to savings of £340 million in the first five years.

Diabetes mortality estimates

The World Health Organization estimated that 1.5 million deaths were directly caused by diabetes in 2012. The World Health Organization's approach for estimating cause-specific mortality was based on statistics obtained from death certificates and reflects reported direct causes of death. The attributable-risk approach used in the IDF Diabetes Atlas allowed a more realistic estimate of the burden of mortality attributable to diabetes, but, at the same time, was based on a set of assumptions. For example, the age- and sex- specific relative risks of mortality in people with diabetes compared to those without were extracted from a small number of studies and findings were applied to other disparate populations. Also, other covariates such as rural or urban environment, time since diagnosis, or medications were not applied in the model

1.5.5Conclusion:

The prevalence of diabetes in adults aged 20–79 years was estimated to be 8.8% in 2015 and predicted to rise to 10.4% in 2040.The high prevalence of diabetes in adults has important social, financial and development implications. There is an increasingly urgent need for governments to implement policies to decrease the risk factors for prediabetes and gestational diabetes, and ensure appropriate access to treatment for all people living with diabetes. Tackling the global impact of diabetes is a monumental task and the IDF continues to act as an advocate for people with diabetes, by educating both individuals and governments on the steps that can be taken for prevention and management of the disease. (9)

1.6 Cause and Effect:

Immunological dysfunction is rarely recognized as a prominent comorbidity of prediabetes in clinics (T2D). Until recently, deadly infections were infrequently met by people in industrialized countries. As a result, increased susceptibility to infection was usually only felt as a small nuisance, such as repeated urinary tract infection. However, as the recent COVID-19 pandemic epidemic shown, patients with diabetes are at an elevated risk of severe consequences when infected with fatal infections such as SARS-CoV-2. Furthermore, even before the corona pandemic, it was widely known that impaired immune cell activity on top of microvascular disease exacerbated hazardous sequelae like as recurrent foot ulcers that can lead to gangrene. This finding suggests that diabetes increases vulnerability to a wide variety of infections and reduces the duration, morbidity, and mortality associated with infectious illness. Diabetes patients are more likely to be infected with CMV and to develop surgical site infections. Clearly, when the immune system is challenged, T2D dysfunction evolves from a small inconvenience to a severe health danger, warranting our attention as health care providers.

1.6.1 Diabetes as a risk factor for infection:

Epidemiology of diabetes and infection:

Patients with T2D are well known to be more prone to infection. In fact, a number of infectious diseases, such as emphysematous pyelonephritis, malignant otitis externa, mucormycotic and Fournier's gangrene are pathognomonic of T2D. However, in addition to these rare conditions, patients with T2D also acquire common infections more frequently. A landmark prospective study from primary care institutions followed up 6.712 T2D patients and 18,911 controls for one year and investigated susceptibility to infection. The authors showed that T2D patients had a higher risk of lower respiratory tract infections (odds ratio (OR) of 1.3, confidence interval (CI) 95% 1.11–1.52) urinary tract infections (OR 1.21, 95% CI 1.07–1.38), bacterial infections of skin and mucosa (OR 1.32, 95%CI 1.13–1.55) and fungal infection (OR 1.41, 95% CI 1.24–1.61). In 2011, a meta-study of 97 prospective cohort studies was published in which 123.205 cause-specific deaths were reported among 820.900 people. This revealed that T2D is associated with a significant increase of infection-related death when pneumonia was excluded (Relative Risk (RR) of 2.39, CI 95% of 1.95–2.93) and also of pneumonia itself (RR 1.8, CI 95% of 1.71–1.9). Importantly, T2D is not only associated with susceptibility to infection, but also with the course and duration of these diseases and with an increased risk of complications. A study comparing bloodstream infections of 71 patients with and 252 patients without diabetes patients showed that the former group had a longer stay at intensive care (RR 7.1, 95% CI of 2–25), longer mechanical ventilation (RR 8.4, 95% CI 1.2–57) and higher chance of renal or hepatic

failure (RR 8.2, 95% CI of 1.6–43). Similar observations were made for a broad range of other infectious diseases. For example, a systematic review of 13 observational studies showed that people with T2D have an RR of 3.11 (CI 2.27–4.26) to develop tuberculosis compared to healthy controls

Normal endocrine control of immune cell function

To better understand how diabetes affects the immune system, it is important to grasp how the endocrine system regulates immune cell functionality under healthy conditions. The immune system puts a major drain on systemic resources and can use up to 30% of all the body ‘s nutrients in circulation upon infection. Whereas the metabolism of immune cells is mostly regulated by cytokines, they are not exempt from endocrine control. Notably, many hormone receptors share intracellular signaling components with those of immune receptors, indicating an overlap in function. Of major importance for endocrine control of immune cells are the hormones leptin and adiponectin produced by adipose tissue. Leptin secretion positively correlates with adipose fat content, and it provides the body with signals that suppress satiety and increase energy expenditure. In addition, leptin plays a role in regulation of blood glucose levels in concert with insulin as it lowers glycemia, insulinemia and insulin resistance. Injection of leptin in streptozotocin (STZ) treated, hyperglycemic rats and mice was shown to lower blood glucose levels independently of food intake. In humans, leptin levels positively correlate with IR independently of BMI and patients with T2D often have high levels of leptin in addition to hyperinsulinemia

During starvation, when adipose triglyceride stores are low, fat cells produce more adiponectin to signal nutrient scarcity. Adiponectin shares some functional properties with insulin, as it promotes glucose uptake and impairs hepatic gluconeogenesis. In immune cells, adiponectin inhibits activation of NF-dB and promotes production of the anti-inflammatory mediators IL-10 and IL-1Ra by macrophages. High levels of adiponectin therefore reduce immune cell responsiveness. Human T cells stimulated with adiponectin were shown to have reduced antigen-specific expansion. Animals deficient for this adipokine showed increased T cell activation upon infection with Coxsackie virus. In the immune system, adiponectin therefore functions as an anti-inflammatory cytokine which lowers its energy expenditure.

Molecular basis of anti-viral immune dysfunctions in T2D:

Several factors play a role in impaired anti-viral immune cell function in the context of T2D, but hyperglycemia appears to be one of the key mediators. The level of glycated

hemoglobin(HbA1c) was shown to positively correlate with the duration and severity of infection with several pathogens. A large retrospective case-control study including > 34.000 patients with pneumonia and > 342.000 controls over an 8-year period revealed a relative risk of 1.23 (CI 1.19–1.28) for patients with T2D. Importantly, the risk was significantly higher for patients with T2D with an HbA1c > 9% (RR 1.60, CI 1.44–1.76) compared to those with HbA1c < 7% (RR 1.22, CI 1.14–1.30) . A similar study recruited 4.748 patients with Type 1 diabetes (T1D) and 12.954 controls. People were divided based on five categories of glycemic control (HbA1c < 7%, 7–7.9%, 8–8.9%, 9–9.9% and > 10%), with a follow-up of 14 years. Also in this study, incidence of infection was significantly higher in patents with T1D compared to controls and the frequency of infection positively correlated with the percentage of HbA1c in the blood. Increased blood glucose levels were shown to impair immune cell function in humans and mice. Hyperglycemia in mice induced by injection of STZ, a model for insulin dependent diabetes, caused a decreased ability of macrophages to be activated in response to infection with *Mycobacterium tuberculosis* (TB). This impaired recruitment of neutrophils, reduced DC activation and lowered cytokine production by these cells. An increase in blood glucose levels was associated with impaired cytotoxicity and cytokine production of CD4 and CD8 T cells and NK cells in patients with T2D following infection with TB. Importantly, T2D has a profound, negative impact on innate immune cell function. For example, granulocytes isolated from patients with T2D were shown to undergo NET-mediated apoptosis, thus impairing wound healing. In addition, production of pro-inflammatory cytokines such as IL-2 and IL-6 was shown to be impaired in peripheral blood mononuclear cells stimulated under hyperglycemic conditions. Finally, hyperglycemia was shown to be of direct benefit for replication of several pathogens which further impedes the ability of the immune system to fight infection under these conditions.

Conclusion: ??????????????

Normal infection protection is mediated not just by specialized immune cells, but also by tissues' innate capacities to provide barriers against pathogens and indicate their infection to the immune system. Diabetes inhibits the ability to respond appropriately to infection at practically all levels of control (Fig. 1).

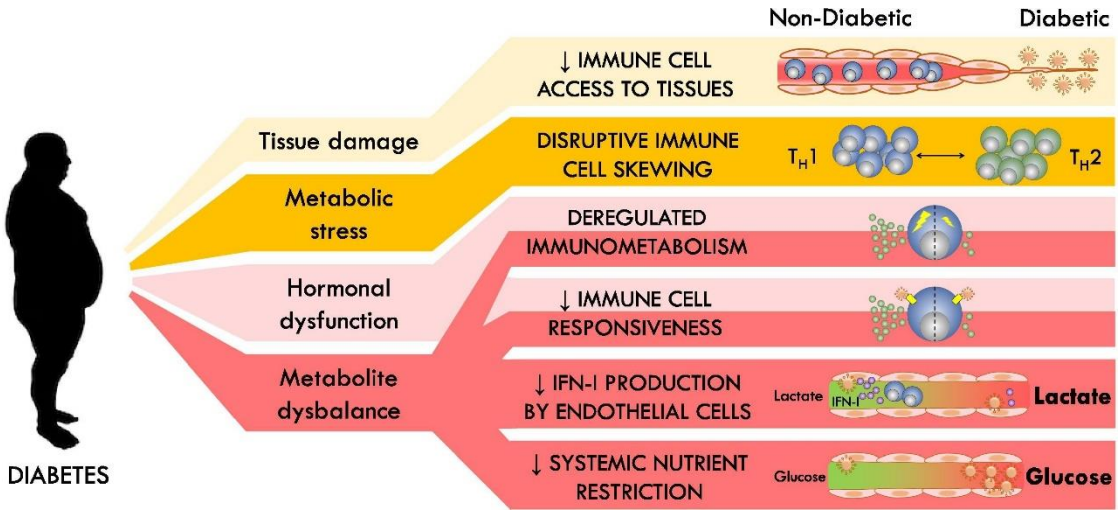

Fig. 1.5. Negative impacts of T2D on immunological control of viral infection

1.6.2 Infection as a risk factor for diabetes

Epidemiology of infection and diabetes

Communication between the endocrine and immune systems is not unidirectional. In response to pathogens such as Influenza A or SARS-CoV-2, we become weak, stop eating, get a temperature and generally feel miserable. This is because the immune system changes normal endocrine regulation of key metabolic processes in our body. Recent data indicates that the physiological changes in metabolism in response to infection may be a trigger for permanent deregulation of blood glucose levels. Many diabetologists will have anecdotal evidence that newly diagnosed patients with T2D had experienced infection in their recent history. In fact, international guidelines recommend screening for infection in newly diagnosed patients, especially if blood glucose levels are very high. Infection was recognized as a cause for increased insulin resistance almost 80 years ago. However, population studies to support this hypothesis have only recently started to emerge.

Because T2D negatively impacts the immune response, it is difficult to determine whether a higher prevalence of infection in patients with T2D is the cause or the result of this disease. Nevertheless, ample evidence is available that infection negatively impacts systemic insulin sensitivity. Infection with viruses such as Influenza A, cytomegalovirus and herpes simplex were all shown to reduce systemic insulin sensitivity. Hyperinsulinemia, euglycemic clamping in patients with a number of respiratory and gastrointestinal infections revealed that insulin resistance was increased in patients, sometimes for more than three months after infection .

Whether infection is a risk factor for development of T2D is mostly shown for chronic viruses. A population-based matched case-control cohort study in Korea selected 576 patients infected with

cytomegalovirus (CMV), but without T2D and 2.880 matched controls without either condition and followed them for 5 years for development of new onset T2D . The authors showed that the case group had a much higher frequency of new-onset T2D (5.6% vs. 2.2% $p < 0.001$). Importantly, subgroup analysis revealed that patients with refractory disease had a significantly higher incidence rate (OR 4.01 95% CI 1.76–7.69) than people with non-refractory disease (OR 1.77 95% CI 1.07–2.82) or with non-infected controls (reference population). In addition to CMV, chronic hepatitis C virus was shown to increase the prevalence of T2D, as well as many hepatic manifestations of metabolic syndrome, such as dyslipidemia, non-alcoholic fatty liver disease and hepatocellular carcinoma. Whether acute viruses are also a risk factor for development of T2D remains to be established, though a recent global initiative has started to determine this for COVID-19.

In summary, many infections are able to induce insulin resistance at least transiently, but whether all are a risk factor for development of T2D still requires confirmation.

Inflammation and diabetes:

Whereas the link between infection and diabetes is relatively new, the impact of inflammation on insulin resistance is well explored. Almost 30 years ago it was discovered in preclinical models of diabetes that if animals were deficient for the cytokine TNF, they did not develop insulin resistance. Since many cytokines were shown to have a negative impact on systemic insulin sensitivity, including IL-1β, IFNγ and IL-6. People with T2D were shown to have a chronic presence of pro-inflammatory cytokines in their circulation, indicative of low-grade inflammation. Neutralization of pro-inflammatory cytokines such as TNF, IL-1β and IL-6 using monoclonal antibody treatment was shown to improve insulin sensitivity in patients with T2D. Notably, patients with T2D have a type-I cytokine profile, which is typically associated with viral infection. The requirement of a specific cytokine environment is also likely the reason that the prevalence of T2D is higher in some inflammatory diseases, such as psoriasis, ulcerative colitis and vasculitis, but not in others such as Crohn’s disease

Proper metabolic regulation is essential for survival. Not unexpectedly, the endocrine system restricts the metabolic activity of nutrient-rich cells like those in the immune system. At the same time, metabolic modulation is a useful tool in the battle against infection. As a result, the immune system adjusts this fundamental system to create a state of systemic preparation for infection, increasing the chances of survival in the face of a potentially lethal threat. Not surprisingly, disruption of normal metabolic control in the context of T2D has a major impact on

the body's ability to respond properly to infection, leading to a large increase in morbidity and death in response to deadly viruses like SARS-CoV-2.

It is therefore important that we do not only acknowledge the pathology of immune-endocrine interactions in diabetes, but also try to understand the physiology behind the processes that regulate insulin sensitivity and blood glucose levels during changes in homeostasis, such as after infection (Fig. 2). Only then can we properly target this mechanism to reduce insulin resistance in diabetes and enhance the immune response if a patient with diabetes suffers from infection.

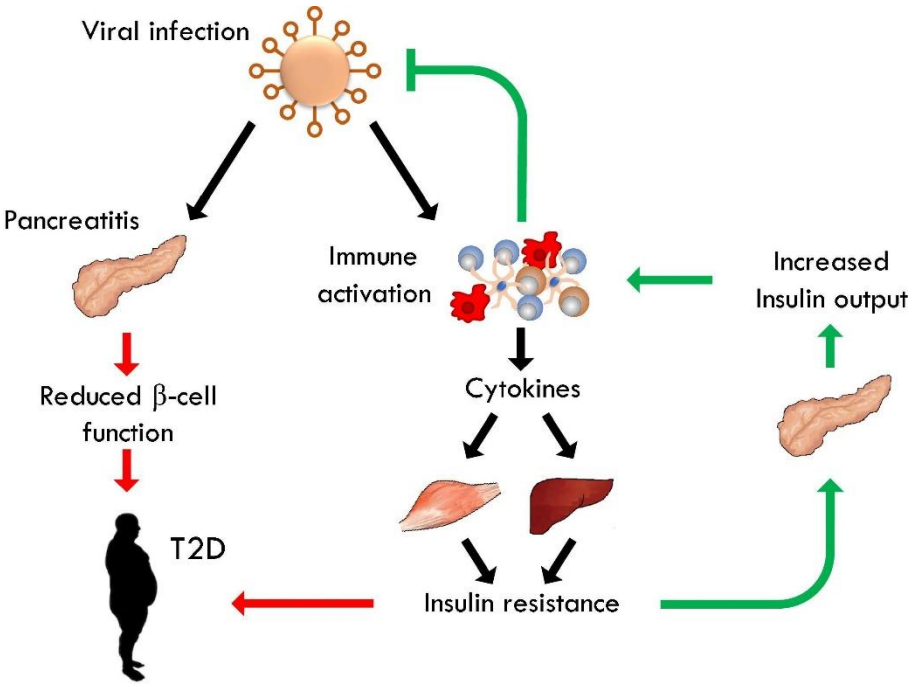

Fig. 1.6: Pre-diabetic effects of viral infection

Viral infection activates a Type-I immune response, resulting in the production of cytokines such as TNF, IFNγ and IL-6. These induce transient insulin resistance in muscle and liver. The pancreas compensates IR through increased secretion of insulin, which directly promotes the antiviral immune system. In obesity, cytokine-induced IR can contribute to the formation of IR. In addition, several viruses infect the pancreas, which negatively impacts its ability to produce insulin. This may also contribute to loss of pancreatic β-cell function.

Enhancing immunity in patients with T2DM

Anti-diabetic treatment does appear to reduce the risk of infection in patients with T2D. Following infection, the severity of disease negatively correlates with the level of glycemic control. Patients with T2D with well controlled blood glucose levels had a significantly lower chance of death than poorly controlled patients following infection with SARS-CoV-2. In

addition, in a cohort study based on a health screening program in Taiwan including 118.645 people with a median follow-up of 8.1 years, it was shown that the level of fasting plasma glucose positively correlated with both the incidence of infection and the risk of infection-associated mortality. (9)

1.7 Why young adult face this problem?

Several research have investigated the frequency of eating problems in adolescent girls and young adult women with type 1 diabetes. Eating disorders, including subthreshold and clinical (full syndrome) eating disorders, as well as milder behavioral problems, are common in young women with diabetes and are linked to poor metabolic control and increased long-term diabetes morbidity and mortality. However, the findings of studies comparing the prevalence of eating disorders in adolescent girls and adult women with type 1 diabetes to that of their non-diabetic peers have varied significantly. The results of these research appear to be strongly influenced by the population analyzed, the technique used, and the diagnostic criteria for eating disorders used.

A few studies have looked at the prevalence of diabetes in clinical samples of eating disorder patients. Not surprisingly, almost all have failed to demonstrate a high prevalence of type 1 diabetes. However, the bulk of research that have investigated eating psychopathology in diabetic populations have yielded more disparate results. While some of these studies found similar rates of eating disorders to those found in non-diabetic populations, others found much greater rates.

Most early studies relied on self-report measures rather than formal interviews to diagnose eating disorders, and no control groups were included. Furthermore, all of these studies had rather small samples of female diabetic participants in the age range at highest risk for eating disorders namely, older adolescence and young adulthood. This has limited their generalizability and power to detect meaningful differences.

1.7.1 Effects of Eating Disorders in Adolescent Girls and Young Women With Type 1 Diabetes:

Several research have been conducted to investigate the prevalence of diabetes in clinical samples of eating disorder patients. Almost all, predictably, have failed to reveal a high

prevalence of type 1 diabetes. However, the majority of studies on eating psychopathology in diabetic groups have produced more varied outcomes. While some of these studies showed eating disorders at similar rates to those seen in non-diabetic populations, 34–37 others found significantly higher rates.

To diagnose eating disorders, most early research relied on self-report measures rather than official interviews, and no control groups were included. Furthermore, all of these studies had rather small samples of female diabetic patients in the age group most vulnerable to eating disorders. (11)

Aims & Objectives of the study

1. To investigate the prevalence of prediabetes-like symptoms predisposition rate in Bangladesh's young adult and adult populations.
2. The relationship between age and gender and these disorders
3. To investigate young adult prediabetes symptoms
4. To evaluate recent condition of health of young adults

Chapter 2

Literature Review

2.1: Prediabetes diagnosis and treatment:

A study was done by Nidhi Bansal about Pre-diabetes diagnosis and treatment (Bansal N. Prediabetes diagnosis and treatment: A review. World journal of diabetes. 2015 Mar 15;6(2):296.). According to his journal the diagnostic criteria for prediabetes are not universal across many worldwide professional organizations, it remains a high-risk state for developing diabetes, with a yearly conversion rate of 5% – 10%. Observational evidence supports a link between prediabetes and diabetic sequelae such as early nephropathy, small fiber neuropathy, early retinopathy, and an increased risk of macrovascular disease. Several studies have demonstrated the efficacy of lifestyle treatments in diabetes prevention, with a relative risk reduction of 40% to 70% in persons with prediabetes. While there is growing evidence that pharmacotherapy is effective in preventing diabetes in adults with prediabetes, pharmaceutical treatment options other than metformin are linked with side effects that limit its usage for prediabetes. There have been no reports of systematic evaluations of health outcomes in children with prediabetes. The effects of prediabetes medication on growth and pubertal development in children are uncertain. Secondary intervention with metformin pharmacotherapy is urged for high-risk individuals, although the criteria for such consideration remain unclear, including the value of early intervention, long-term cost effectiveness of such therapies, and the end point of therapy.

2.2 Diabetes Anticipated into people in 2015:

Another study was done by Aditya K.KhetanMDJournal of Cardiology. 2018 May 1;34(5):615-23.) His journal explained that diabetes is anticipated to increase from 415 million people in 2015 to 642 million people by 2040. Most people go through a period of prediabetes before getting full-blown diabetes. The pathophysiology of prediabetes is dominated by insulin resistance, poor incretin activity, and insulin hypersecretion. Adults over the age of 40, as well as other high-risk individuals, should be tested for diabetes using fasting plasma glucose and/or hemoglobin A1c. The goal of treatment for patients with prediabetes should be to restore

euglycemia, because there is evidence that restoring normoglycemia during prediabetes and early diabetes can result in long-term remission.

2.3 The epidemiological evidence of pre-diabetes:

Another study was done by Justin B. Echouffo-Tcheugui and Elizabeth Selvin about The epidemiological evidence of pre-diabetes (Echouffo-Tcheugui JB, Selvin E. Prediabetes and what it means: the epidemiological evidence. Annual review of public health. 2021 Apr 1;42:59-77.) It shows that Prediabetes is a common condition that occurs between normal glycemia and diabetes. It is more common in older people and obese people. In current practice, five alternative definitions of prediabetes are utilized, each based on different HbA1C, fasting glucose, and 2-hour glucose cut points. A key issue for the discipline is a lack of information on when one definition is preferable to another. The risks of significant problems in people with prediabetes, such as diabetes, cardiovascular disease, kidney disease, and death, differ depending on the definition of prediabetes used. Randomized clinical trials have shown that lifestyle and pharmaceutical treatments can be cost-effective in preventing diabetes and improving cardiovascular risk factors in prediabetic persons.

2.4 Metabolomics in Prediabetes and Diabetes:

Another study was done by Marta Guasch-Ferré about Metabolomics in Prediabetes and Diabetes (Guasch-Ferré M, Hruby A, Toledo E, Clish CB, Martínez-González MA, Salas-Salvadó J, Hu FB. Metabolomics in prediabetes and diabetes: a systematic review and meta-analysis. Diabetes care. 2016 May 1;39(5):833-46.). According to their journal They found 27 cross-sectional studies and 19 prospective studies that reported links between metabolites and prediabetes and/or prediabetes Individuals with prediabetes had greater levels of carbohydrate (glucose and fructose), lipid (phospholipids, sphingomyelins, and triglycerides), and amino acid (branched-chain amino acids, aromatic amino acids, glycine, and glutamine) metabolites. Blood concentrations of various metabolites, including hexoses, branched-chain amino acids, aromatic amino acids, phospholipids, and triglycerides, were linked to the prevalence of prediabetes and prediabetes in prospective studies. They meta-analyzed data from eight prospective studies that gave metabolite and prediabetes risk estimations, involving 8,000 people, 1,940 of whom had prediabetes.They discovered a 36 percent increased risk of prediabetes per study-specific SD difference for isoleucine (pooled relative risk 1.36 [1.24–1.48]; I2 = 9.5 percent), a 36 percent increase for leucine (1.36 [1.17–1.58]; I2 = 37.4 percent), a 35 percent increase for valine (1.35

[1.19–1.53]; I2 = 45.8 percent), a 36 percent increase for tyrosine (1 Glycine and glutamine were found to be inversely related to the risk of prediabetes (0.89 [0.81–0.96] and 0.85 [0.82–0.89], respectively; both I2 = 0.0 percent).

2.5 Prediabetes and associated disorders:

A study was done by Martin Buysschaert, about Prediabetes and associated disorders (Buysschaert M, Medina JL, Bergman M, Shah A, Lonier J. Prediabetes and associated disorders. Endocrine. 2015 Mar;48(2):371-93.). It shows that Prediabetes is defined as an increase in plasma glucose over the normal range but less than that of clinical diabetes. Individuals with prediabetes have IFG, IGT, IFG with IGT, and high HbA1c values. This condition is distinguished by insulin resistance and -cell dysfunction. The diagnosis of prediabetesis is critical since both IFG and IGT are well-known risk factors for prediabetes, with a higher risk in the presence of both. Furthermore, as this analysis will demonstrate, prediabetes is connected with related illnesses that are normally only examined in patients with developed diabetes. Cardiovascular illness, periodontal disease, cognitive dysfunction, microvascular disease, blood pressure irregularities, obstructive sleep apnea, low testosterone, metabolic syndrome, different biomarkers, fatty liver disease, and cancer are examples of these. Because the vast majority of people with prediabetes are unaware of their illness, it is critical that the related problems be diagnosed, especially in the context of mild hyperglycemia, so that they can benefit from early care.

2.6 Phenotypes of prediabetes and stratification of cardiometabolic risk

Another study was done by ProfNorbertStefanMD[acd] about Phenotypes of prediabetes and stratification of cardiometabolic risk (Stefan N, Fritsche A, Schick F, Häring HU. Phenotypes of prediabetes and stratification of cardiometabolic risk. The lancet Diabetes & endocrinology. 2016 Sep 1;4(9):789-98.). It shows that Prediabetes is linked to an increased risk of prediabetes, cardiovascular disease, dementia, and cancer, and its incidence is rising globally. In persons with prediabetes, lifestyle and pharmaceutical therapies can help avoid the development of diabetes and possibly cardiovascular disease. However, prediabetes is a highly diverse metabolic state in terms of etiology and illness prediction. Improved understanding of these characteristics, as well as precise phenotyping of prediabetes, could aid in disease risk categorization. The extreme metabolic phenotypes of metabolically healthy obesity and metabolically unhealthy normal

weight, insulin secretion failure, insulin resistance, visceral obesity, and non-alcoholic fatty liver disease are the emphasis of this Personal View.

2.7 Treating prediabetes with metformin:

Another study was done by Muriel Lily and April 2009, 55 (4) 363-369 about Treating prediabetes with metformin. It explained to see if metformin could prevent or delay the establishment of prediabetes mellitus in persons with prediabetes (impaired glucose tolerance or impaired fasting glucose).From January 1966 to the present, MEDLINE was searched, and articles fulfilling the selection criteria were hand searched.

Individuals with poor glucose tolerance or impaired fasting glucose were included in randomized controlled trials involving metformin treatment to postpone or prevent prediabetes. Diabetes development was a needed outcome measure, with a minimum 6-month follow-up period. These criteria were met by three research.

The ethnicity of the group investigated, the rates of conversion to diabetes from prediabetes, and the dose of metformin administered differed among the three investigations. In general, the studies were well-conducted, however two of the three did not conduct full intention-to-treat analyses.A sensitivity analysis was carried out by converting all data to intention-to-treat data and assuming the worst-case scenario for those who were lost to follow-up.

Metformin slows the progression of prediabetes to diabetes. This was true at greater and lower doses (850 mg twice day and 250 mg twice or three times daily), in people of various ethnicities, and even when a sensitivity analysis was performed on the data. For treatment over a three-year period, the number needed to treat ranged between 7 and 14.

2.8 Medical Cost Associated with Prediabetes:

Another study was done by Yiduo Zhang about Medical Cost Associated with Prediabetes They estimate national health care resource utilization and medical expenses related with prediabetes (PD) in 2007 using either a fasting plasma glucose of 100 to 125 or an oral glucose tolerance test of 140 to 200.

They evaluate patterns of health care resource utilization by Parkinson's disease status using Poisson regression with medical claims from an adult sample that was continuously insured

between 2004 and 2006. We estimate the amount of national health resource use related with PD by combining rate ratios that represent health care use patterns with national PD prevalence rates from the National Health and Nutrition Examination Survey. According to the data, Parkinson's disease is associated with significantly increased rates of ambulatory visits for hypertension, as well as endocrine, metabolic, and renal problems. There is no evidence that Parkinson's disease is connected with an increase in emergency visits or inpatient days. Extrapolating these tendencies to the 57 million individuals with Parkinson's disease in 2007, the national annual medical expenses of PD surpass $25 billion, or $443 more for each adult with PD.

Excessive utilization of ambulatory services for diabetes-related comorbidities is associated with Parkinson's disease. Our findings reinforce the business case for lifestyle treatments to prevent diabetes by introducing new economic benefits that could be realized by avoiding or delaying PD. (2009, Population Health Management, 12:157-163)

2.9 Peripheral neuropathy in prediabetes and the metabolic syndrome:

Another study was done by Amro M Stino,Albert G Smith about Peripheral neuropathy in prediabetes and the metabolic syndrome It explains that Peripheral neuropathy is a leading cause of disability globally. Diabetes is the leading cause of neuropathy, accounting for half of all cases. Diabetic peripheral neuropathy (DPN) affects more than half of all diabetics and is a primary cause of poor quality of life due to pain, sensory loss, gait instability, fall-related damage, and foot ulceration and amputation. The majority of non-diabetic neuropathy patients have cryptogenic sensory peripheral neuropathy (CSPN). A increasing body of research linked prediabetes, obesity, and metabolic syndrome to an increased risk of DPN and CSPN. This link may be more prominent in prediabetes patients. There are no effective medicinal treatments for CSPN or DPN, and intensive glycemic control is only beneficial in reducing neuropathy risk in type 1 diabetes.

2.10 Treating prediabetes:

Another study was done by Minerva Medica, 29 Oct 2018, 110(1):52-61 about Treating prediabetes .It shows that Prediabetes is defined as a subclinical decrease in fasting plasma glucose or decreased glucose tolerance, or both. The degree of impairment is intermediate between euglycemia and hyperglycemia in prediabetes Prediabetes is not regarded innocuous

because it not only increases the incidence of T2DM but is also linked to micro and macrovascular problems. First-line therapies include lifestyle modifications such as diet and exercise. Biguanides (metformin), alpha-glucosidase inhibitors (Acarbose), pancreatic lipase inhibitors (Orlistat), PPAR-gamma agonists (Rosiglitazone, Pioglitazone), meglitinides (Nateglinide), and GLP-1 receptor agonists (Liraglutide) have all demonstrated benefits in randomized controlled studies. Another effective method of avoiding T2DM in adults with prediabetes and obesity is bariatric surgery.Prediabetes, in its different forms, is a risk factor for the development of T2DM and diabetic problems in the future. Importantly, the prediabetic state is responsive to therapies that can prevent or delay the progression to overt T2DM. There are knowledge gaps about how to make prognosis highly sensitive and specific as to which patients would acquire T2DM.

Chapter 3

Methodology

3.1Participants:

The 153 healthy participants were primarily undergraduate students (77 percent) from various departments and varied jobholders (23 percent) from various areas of Bangladesh. They were randomly selected, right-handed, and classed as n=75 female (50 percent) and n=78 male (50 percent). Male and female participants ranged in age from 18 to 31 years The participants were mostly frequent computer and other digital device users who had been using these devices for 5-10 years (44%), >10 years (31%), 2-4 years (21%), and 2 years (4 percent). The following criteria were used to select participants:

i. Everyone above the age of 18; and

ii. Both sexes, regardless of occupation.

The individuals were excluded based on several characteristics like as

1. Polycystic ovary syndrome
2. Level of LDL
3. Unintended loss of weight

a

3.2 Materials and Procedures:

During the data collection phase, the cross-sectional and random sampling study methods were used. The survey period began on 5 February and ended 03June2022. To complete the study on time, a work schedule was created based on the various study activities. The topic selection and procedure preparation took about two weeks. The following months were devoted to data collecting, analysis, and report writing.

From the survey necessary information are added such as name, age, gender, height, and so on. For thesis purposes, one unusual question was added: waist size.

Then we included additional informative questions such as increased thirst, frequency of urination, exhaustion, hazy vision experience, numbness and tingling, frequent infections and sluggish healing process, weight loss, and so on.

The cross-sectional and random sample study methods were used to acquire data. The survey was carried out online using a Google form. For the participants, a questionnaire was created. The questionnaires were short and to the point. The Google form was designed in such a way that no question could be skipped without an answer. The questions were designed in such a way that participants could simply offer answers.

Chapter 4

Results and Discussion

Result:

4.1 Response on Thirst Condition:

Among the 153 participants, 74.3 percent said their thirst level had recently increased, whereas 25.7 percent said their thirst level had not recently increased.

Excessive thirst, caused by elevated blood sugar levels, is a well-known sign of both prediabetes and diabetes. A substantial amount of glucose is discharged in the urine when blood glucose levels are high. Because urine contains so much glucose, it draws water, increasing thirst. The majority of people acquire Type 2 diabetes within 10 years after being diagnosed with prediabetes. This means there is still time to prevent this from happening. Prediabetes, on the other hand, may be reversed in about three years.

So drinking more than 6L of water each day is unquestionably a problem.

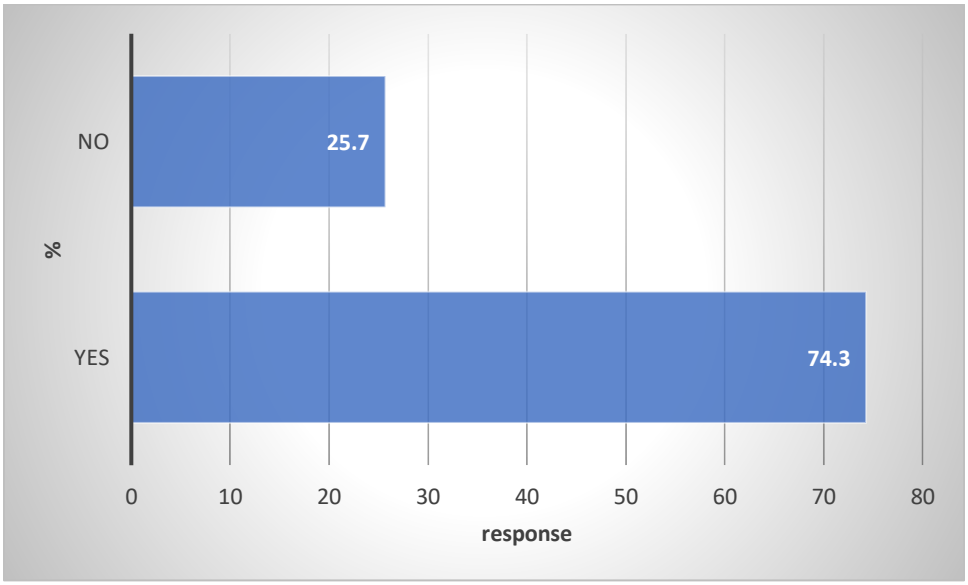

Fig 4.1: Response on Thirst Condition:

4.2 Response on Blur Vision condition

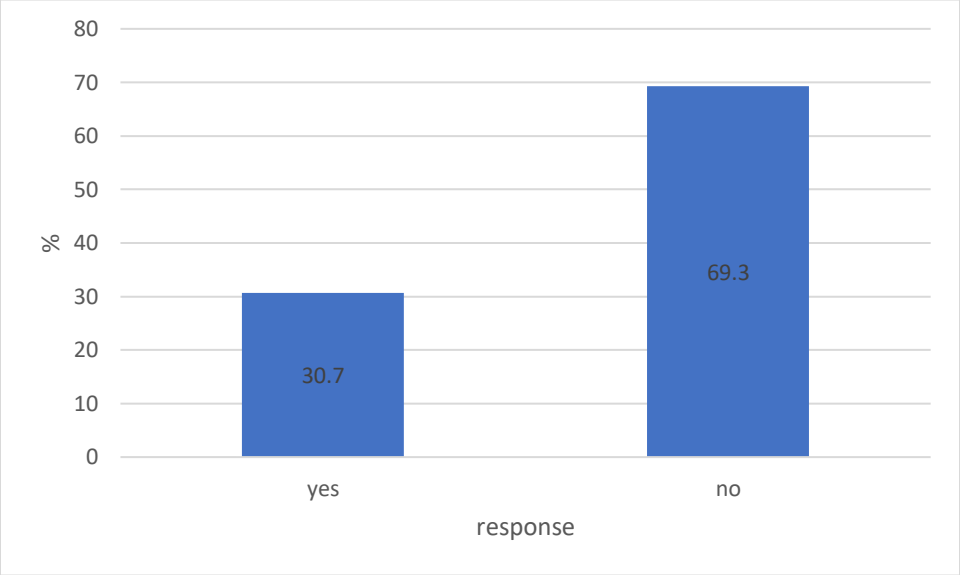

Fig 4.2: Response on Blur Vision Condition

The proportion of participants with blurred vision is 30.7 percent, which is about half (69.3 percent) of the total.

One of the most prevalent symptoms of diabetes is impaired vision. If you have visual problems, you should check your blood sugar levels because many people with prediabetes already have diabetic issues.

Young persons are at lower risk of developing prediabetes and diabetes mellitus.

4.3 Response on Family History

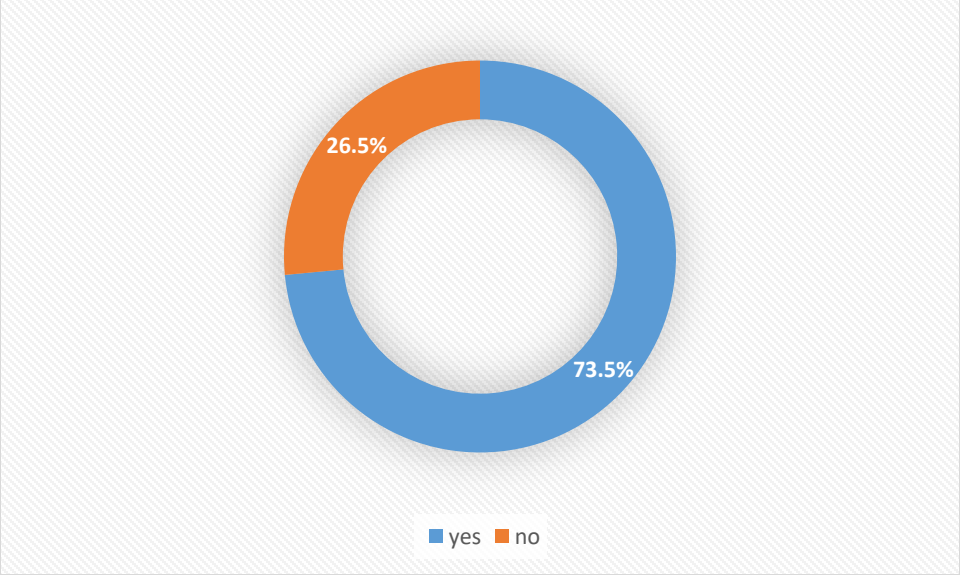

Fig 4.3: Response on family History

73.5 percent of individuals had a diabetes patient in their family tree, whereas 26.5 percent do not.

According to a research of over 8,000 participants, those with a family history of diabetes have a 26% greater chance of prediabetes. Family medical history is valuable for genomic research because it characterizes the complex interaction of environmental, behavioral, and genetic variables. People with a family history of diabetes are more likely to have prediabetes and develop diabetes.

Three quadrants are at risk for prediabetes and diabetes mellitus, which is insufficient.

4.4 Response on wound Healing:

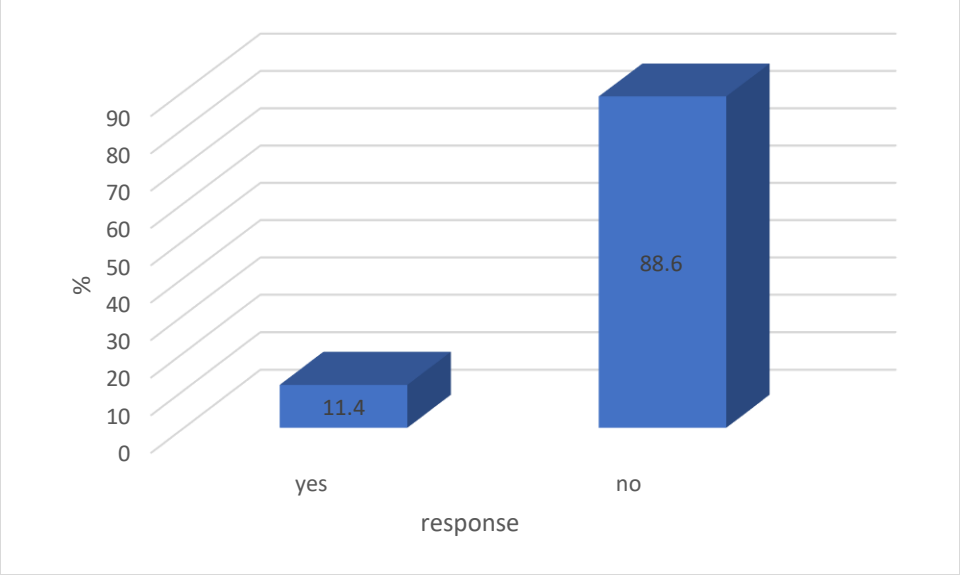

Fig 4.4 Response on Wound Healing

Only 11.4 percent of people have frequent infections and a slow healing process, whereas 88.6 percent do not.

Slow wound healing can be a marker of prediabetes, especially when combined with other signs and symptoms. If the body has difficulty metabolizing carbohydrates, high blood sugar levels might result. This might impair the body's capacity to heal wounds. Wounds heal more slowly and develop more swiftly in diabetics, so knowing what to look for is critical.

This is a wonderful circumstance because the majority of them responded badly to the most prevalent condition of prediabetes and diabetes mellitus.

4.5 Response on Fatigue condition

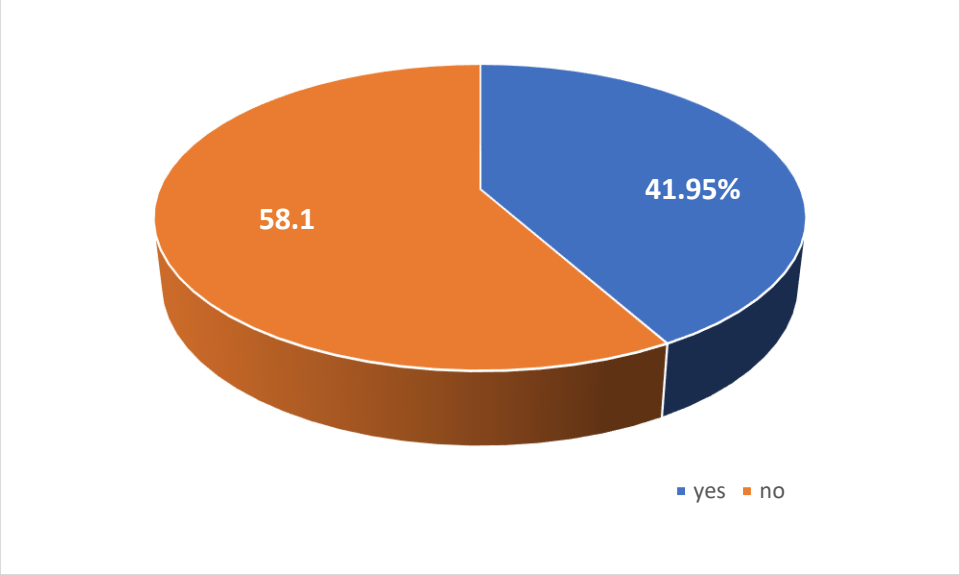

Fig 4.5 Response on Fatigue condition

When asked if they felt tired, 41.9 percent of participants replied affirmatively, while 58.1 percent reacted negatively.

Undiagnosed pre-diabetes is one of the most prevalent causes of chronic mental and physical tiredness. In the United States, an estimated 100 million people have pre-diabetes.

The difference between those who are fatigued and those who are not fatigued is not significant. As a result, half of our young adults are at danger of developing prediabetes or diabetes mellitus.

4.6 Response on recently elevated blood pressure (more than 140/90 mmHg)

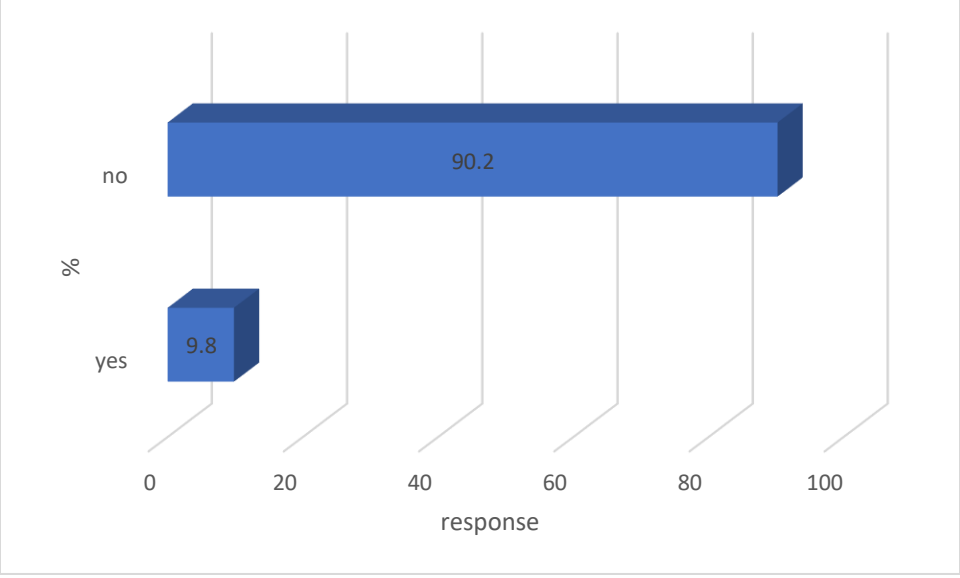

Fig 4.6 Response on recently elevated blood pressure (more than 140/90 mmHg)

Only 9.8 percent of persons have lately had increased blood pressure (greater than 140/90 mmHg), while 90.2 percent are not affected.

Prediabetes is intimately connected to high blood pressure. High blood pressure patients are more prone than normal blood pressure patients to develop insulin resistance, prediabetes, and diabetes mellitus.

With increased blood pressure, young adults are not at risk for prediabetes or diabetes mellitus.

Discussion

Prediabetes is a prevalent condition among the young, but they are aware of the signs and measures. We may deduce from the study that people must exercise extreme caution when it comes to their health and physical capacity. They must consume healthful foods, fruits, and plenty of water.

We received 153 replies to our survey, which is insufficient for a good result. If we can collect more than 500 replies, we may have a positive outcome and be able to conclude additional information. As a result, further research is required, as well as the distribution of important educational materials to young adults.

Vitamin D's extra-skeletal effects have piqued people's curiosity. A plethora of human clinical studies have been conducted to investigate the potential relationship between vitamin D metabolite levels and glycemic management and the occurrence of diabetes. Interventions to enhance 25-hydroxyvitamin D have been reported to lower blood pressure in groups at risk of cardiovascular disease in a number of modest supplementation studies. There is additional

evidence that vitamin D supplementation improves poor glucose tolerance and insulin resistance in prediabetespatients. We discovered that a short course of vitamin D treatment reduced blood pressure in prediabetesindividuals in our study. Indeed, vitamin D metabolites have been linked to blood pressure management.Interestingly, observational studies have found that blood pressure rises in the winter, indicating that low UV exposure and consequently a reduced ability for cutaneous vitamin D production are linked to high blood pressure. The most notable mechanism linking vitamin D to high blood pressure is its role as a negative regulator of the renin-angiotensin system; however, other notable hypotheses have suggested that vitamin D affects vascular endothelial function or intracellular calcium concentrations in vascular smooth muscle. Gupta et al. discovered that vitamin D levels had an inverse relationship with circulating renin and angiotensin II, indicating a mechanism for blood pressure increase. Furthermore, vitamin D administration tends to lower blood glucose and blood pressure. Low serum vitamin D levels are likely to increase the risk of prediabetes and high blood pressure. Figure 4.1 demonstrates that among 153 answers, thirst did not grow fast, however in Figure 4.2, urination rose among young people. Figure 4.3 illustrates that the amount of obscured vision rose gradually. The combination of various testing methodologies laid the groundwork for a better understanding of the initiation of dysfunctional physiological processes within OOI, PD, and T2D populations at the start of illness onset, providing light on connections between symptoms and disorders. There were moderate positive associations between the 1 g monofilament and total and left leg scores and the recorded SNAP values. Furthermore, overall QOL-DN, ADLS, and symptom scores were adversely and moderately connected with SNAPs, whereas small fiber scores were negatively and moderately correlated with SNCV. These associations imply that these methods might be beneficial for low-cost screenings.Other studies have shown different results, which may be explained in part by variations in the populations tested. Perkins et al. only studied individuals with documented diabetes prediabetesbut our study included seemingly healthy individuals selected for our OOI group who may be prone to DPN, as well as adults with Parkinson's disease and prediabetesOthers have not observed such a high incidence of bilateral, aberrant results in 71 percent of the subjects in our research.

Chapter 5

Conclusion

Conclusion:

Diabetes is a slow-killing disease with no known cure. However, its complications can be avoided with proper education and prompt treatment. Blindness, kidney damage, and heart attack are three major complications. To avoid complications, patients' blood glucose levels must be strictly controlled. One of the difficulties with tight control of blood glucose levels is that such attempts may result in hypoglycemia, which causes far more severe complications than an increased level of blood glucose. Researchers are now looking for new ways to treat diabetes. The purpose of this paper is to provide a general overview of the current state of diabetes research. The author considers diabetes to be one of the most challenging research topics of the twenty-first century and wishes to encourage new researchers to take on the challenges.

There is still a need for a systematic evaluation of the health outcomes of prediabetes and any benefits from early treatment. It is critical to select the appropriate outcomes for such a study. Furthermore, the criteria used to define prediabetes must be refined in light of long-term medical outcomes. While these studies appear to be necessary, the length of time required to study the negative outcomes of prediabetes, as well as the low frequency of some of these outcomes, may be a limiting factor for such studies. There is currently insufficient evidence to develop clinical guidelines for the treatment of prediabetes. Lifestyle interventions continue to be an important part of prediabetes management. Pharmacotherapy should be used on an individual case-by-case basis. When pharmacotherapy is used to treat prediabetes, the physician should initiate a treatment plan with predefined goals and end points. Pharmacotherapy should be used with caution in children and adolescents.

Chapter 6

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