Introduction

Chapter I: Introduction

Prediabetes is a state of hyperglycemia which consists of Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) both of which are characterized by abnormal increases in plasma glucose which are considered higher than the normal blood glucose values but below the threshold for the diagnosis of diabetes (WHO, 2016. The other alternative names associated with prediabetes involve 'non-diabetic hyperglycemia/intermediate hyperglycemia' (WHO 2016).

Both IGT and IFG play a tremendous role in the field of diabetes. First and foremost, they possess a serious threat to the future development of diabetes. Secondly, both are risk factors for the development and progression to Cerebrovascular Disease (CVD). Thirdly, they play a significant role in the prevention of diabetes through the introduction of future interventions. The risk factors for the progression to Type 2 Diabetes Mellitus (T2DM) from IFG and IGT is related to glucose levels along with weight and age. The 5 years progression rate for the conversion to T2DM from IGT or IFG are estimated to be 26 % and 50% respectively (IDF 2021).

Currently there are approximately 541 million (10.6%) adults worldwide that suffer from IGT, and this figure is projected to increase exponentially to 730 million (11.4%) of all adults in 2045 (IDF 2021).

On the other hand, currently there are approximately 319 million (6.2.%) adults worldwide that suffer from IFG, and this figure is projected to increase exponentially to 441 million (6.9%) of all adults in 2045 (IDF 2021).

A nationwide survey done in the Bangladeshi population, which was conducted in over 83000 patients, the prevalence of diabetes was 9.7% as compared to 22.4% for prediabetes (Akter S et al., 2014). More alarmingly 56% of the population were not aware that they were diabetic. A more recent meta-analysis involving over 56,000 individuals had demonstrated a prevalence of 10.1% for prediabetes in Bangladesh based on the findings of 26 population based studies (Akter S et al., 2020).

In the last 15 years there has been a tremendous increase in the global healthcare expenditures owing to diabetes and its complications in the adult age group (20–79 years). These expenditures are expected to increase further in addition to the direct costs associated with diabetes itself (IDF 2021) .

Although there are rising global healthcare expenditures on diabetes worldwide, only 1% of the total healthcare was spent in the South East Asia (SEA) region despite housing 16.8% of the total global diabetes population (IDF 2021).

These expenditures owing to the increasing diabetic population worldwide will eventually have a substantial and significant impact on health expenditures worldwide and contribute to almost 11.5% of the overall global health spending (IDF 2021).

In a poor resource country like Bangladesh where an alarmingly large number of people are living beyond the poverty line, with the rising healthcare expenditures, limited resources and poor accessibility to both medications and health care professionals with little or no government action to provide free medications or insulin, the struggles of the public are tremendous and detrimental to the basic human rights advocated for the citizens. Even the lab diagnostics and access to health care personal are contributed from the patient's own pockets rather than in the form of government subsidies or initiatives for the benefit of improved access to healthcare. Hence, a significant number of people who are currently under the poverty line or lower, lower middle or middle class patients are finding it exceedingly difficult to make ends meet and purchase their own medications, perform their own laboratory investigations and finance their own routine doctor's consultations.

The disease itself is not only causing problems for the patients but also creates a burden for the family as well. The burden for both patients and their families are due to increased Type 2 DM complications which leads to financial burden decreasing the daily quality of life. In Bangladesh, the average annual cost for diabetic medication was $865 in 2019 which was the highest contributor to the healthcare expenditure followed by the indirect costs of hospitalization due to diabetes complications. The hospitalized patients had to endure 4.2 times higher average annual costs due to diabetes than those without hospitalization (Afroz et al., 2019). These results are higher than previous studies conducted in the Bangladeshi population ($314) and considerably higher than other South Asian countries like India ($525) and Pakistan ($197) which states that the average annual costs for each patient with diabetes are also increasing exponentially (Afroz et al., 2019) .

In addition to urbanization, the main factor for the high prevalence of diabetes and metabolic abnormalities among Asians is the tendency for central obesity and insulin

resistance (Akter S et al., 2014).Asians also have a higher prevalence of prediabetes as compared to their Caucasian counterparts owing to their increasing sedentary lifestyle, adoption of western diets and rapid urbanization. All these factors are strong indicators of obesity and insulin resistance (Naqvi S et al., 2017).

Dyslipidemia and poor glycemic control (increased fasting glucose) are both modifiable risk factors for the development of coronary artery disease in T2DM patients. Diabetic dyslipidemia is characterized by high LDL and low HDL cholesterol as well as high triglycerides. Increased triglyceride levels pose an independent risk factor for the development of T2DM and glucose metabolic disorders. It specifically targets the muscle, adipose tissue, and pancreatic cells to increase the blood glucose levels. It is also an independent risk factor that contributes to non-alcoholic fatty liver disease and metabolic syndrome (Lee T L et al., 2021).

Insulin resistance (IR) is not only a significant contributor to the development of Cerebrovascular Disease (CVD) but also has a strong correlation with the outcomes associated with CVD (Zhang Y et al., 2020).

The Hyperinsulinemic-Euglycemic Glucose Clamp (HEGC) is the gold standard for the evaluation of insulin resistance (DeFronzo RA et al., 1979) but it is a costly procedure, time-consuming and very difficult to operate in large populations or regular clinical settings (Muniyappa R et al., 2008). Other alternative widely used methods for evaluating insulin resistance involves the homeostasis model assessment for insulin resistance (HOMA-IR) index which requires the fasting plasma glucose Matthews DR et al., 1985). However, the HOMA-IR involves Serum Fasting Plasma Glucose or C-peptide assays which are expensive, not easily assessable and has limitations associated with poor reproducibility. So, there is a necessity for newer biomarkers that are more reliable, affordable, and easier to detect in everyday clinical settings (Zhang Y et al., 2020).

So, the search for more inexpensive and equally reliable markers is of paramount importance to ensure effective screening among the patients. The triglyceride glucose (TyG) index is a new risk marker that has been extensively studied in type 2 diabetes patients and has also been suggested as a surrogate marker for insulin resistance owing to its close correlation and enhanced predictability with HOMA-IR . It is measured as the product of the fasting glucose and fasting triglyceride levels and

hence is simple, inexpensive, and a reliable marker in poor resource settings (Du T et al., 2014)

Insulin resistance has been linked to poor glycaemic control, dyslipidemia, hypertension, and advanced atherosclerosis (Bonora E et al. 2002). Concomitantly, TyG has also been identified as a risk marker for Coronary Artery Disease (CAD) (Lee EY et al. 2016) and Non-Alcoholic Fatty Liver Disease (NAFLD) (Zhang S et al. 2017). Studies also suggest a potential role for TyG in diabetes management primarily because of its close association with glycaemic control. Elevated triglyceride levels have been linked to impaired muscle glucose metabolism and can thereby reduce insulin sensitivity (Timalsina S et al. 2021). Additionally, TyG index has a strong correlation with calcification (Park K et al., 2019), stenosis (Lee EY et al. 2016), and stiffness (Lee SB et al. 2018) of the coronary arteries as well as symptomatic CAD (Da Silva A et al. 2019).

The Glycosylated Haemoglobin (HbA1c) level is a relative reflection of the average glycaemic status over the previous 3 months and has been strongly associated with both micro as well as macrovascular complications of diabetes (Laiteerapong N et al., 2019). The frequency of testing depends on several factors like the clinicians advise, follow up protocols in respect to the current clinical status of the patient and modify the treatment regimen accordingly. However, it's use is still limited as a regular screening test owing to its high costs and the availability of standardized lab assays. The OGTT requires more time and involves both fasting and 2 hours 75g post glucose load blood samples and twice the number of venipunctures (Bergman M et al., 2020). There are also certain limitations to the use of HbA1c in clinical settings apart from it being expensive, for instance in demonstrates a variation in protein susceptibility and varies substantially in between different ethnicities and races. HbA1c is also altered in haemoglobinopathies like hemolytic anaemia, chronic malaria, blood loss as well as in pregnancy (Bergman M et al., 2020).

It has also been suggested that TyG index appears to have a stronger correlation than HbA1C and plasma triglyceride levels for the occurrence of cardiovascular events in diabetic patients and is a superior predictive factor (Su WY et al., 2019). Since HbA1c has quite a large no. of afore-mentioned limitations like within-day blood glucose variability especially in relation to hypoglycaemic events and does not reflect

long term dyslipidemic changes, the TyG index can give us a clearer picture in this regard to glycaemic control and variability in dyslipidemic patients. Thus, the author has decided to conduct a study which will not only help to find out a cost-effective screening for prediabetes but also positively correlate with HbA1c as a marker of prediabetes and HOMA-IR as a marker of Insulin Resistance.

Aims and Objectives of Study:

Overall Objectives: To compare the efficacy of Triglyceride Glucose Index and HbA1c as a marker of prediabetes and insulin resistance in a Tertiary Care Hospital in Chittagong

Specific Objectives:

1. To find out a cost-effective screening for prediabetes
2. To check whether Triglyceride Glucose (TyG) index is comparable to HbA1c for screening for prediabetes.
3. To check whether Triglyceride Glucose (TyG) index is comparable to HOMA-IR as a marker for insulin resistance.

Review of Literature

Chapter II: Review of Literature

2.1 Concept of Prediabetes

Prediabetes is a state of hyperglycaemia when an individual's blood sugar level is higher than normal, but the threshold is not enough to be considered as diabetes (Genuth S et al., 2003).

The American Diabetes Association (ADA) has defined prediabetes as IFG and IGT based on the Oral Glucose Tolerance Test (OGTT) where IFG is defined as fasting plasma glucose concentration in the range of ≥5.6 - ≤6.9mmol/L and IGT is defined as elevated 2 hours plasma glucose level in the range of >7.8 - <11.0 mmol/L after a 75g post glucose load on the OGTT. It could also be defined in the parameters of HbA1C in the range of ≥5.7 - ≤6.4% (Chowdhury SR et al., 2018).

However, The World Health Organization (WHO) differs in its definition of IFG to the ADA where it states that IFG is considered as fasting plasma glucose concentration in the range of >6.1 - <6.9 mmol/L while the criteria for diagnosis for IGT remains the same as the ADA (Chowdhury SR et al., 2018).

Moreover, The American Association of Clinical Endocrinologists (AACE) does not recommend the use of HbA1C alone for the diagnosis of prediabetes. The AACE states that HbA1C values in the range of 5.5-6.4% can be used in the screening for prediabetes but additional tests like FPG or OGTT need to be done to confirm the diagnosis. Screening can be done using HbA1c as a reference value (5.5-6.4%) but the confirmation must be determined by additional test like FPG or OGTT (Chowdhury SR et al., 2018).

Prediabetes is associated with a high-risk of developing diabetes related complications like cardiovascular disease, nephropathy, neuropathy in addition with a heightened risk of developing diabetes as well. About 21% of prediabetes individuals will most likely have at least one microvascular complication as shown from the results of The Australian Diabetes, Obesity and Lifestyle Study (AUSDIAB) (Richard EP, et al., 2007).

2.2 Epidemiology and Prevalence of Prediabetes

Currently there are approximately 541 million (10.6%) adults worldwide that suffer from IGT, and this figure is projected to increase exponentially to 730 million (11.4%) of all adults in 2045 (IDF 2021).

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A nationwide survey done in the Bangladeshi population, which was conducted in over 83,000 patients, the prevalence of prediabetes was 22.4% (Akter S et al., 2014). A more recent meta-analysis involving over 56,000 individuals had demonstrated a prevalence of 10.1% for prediabetes in Bangladesh based on the findings of 26 population based studies (Akter S et al., 2020).

2.3 Rationale for the definition of Pre-diabetes

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recognized an intermediate group of individuals whose blood glucose levels were either too high to be considered normal or not enough to be considered as diabetic or have yet to reach the criteria for diabetes. They furthermore identified these groups of intermediate individuals as having Impaired Fasting Glucose (IFG) or Impaired Glucose Tolerance (IGT) (Genuth S et al., 2003).

Those individuals identified with having either IFG or IGT were termed as prediabetes and have a high risk of developing T2DM over the course of time. Both IFG and IGT are independent risk factors for Cardiovascular Disease as well as diabetes. Prediabetes (IFG and IGT) is also linked to obesity (both abdominal and visceral), dyslipidemia (high triglycerides and/or low HDL Cholesterol) and Hypertension as well (Richard EP et al., 2007).

A systematic review consisting of studies from 16 cohorts identified that those individuals with an HbA1c between 5.5-6.0% had a significantly increased risk of developing T2DM with an incidence ranging from 9-25%. Whereas those individuals with an HbA1C between 6-6.5% had an incidence of 25-50% for developing T2DM and a relative risk which was substantially (20 fold) higher than those with an HbA1c of 5.0% (Zhang X et a;., 2010). Subsequently, An HbA1c of 5.7% from other studies

indicate similar diabetes risk as compared to that of those with high risk in the Diabetes Prevention Program (DPP).

Hence an HbA1C range of 5.7 to 6.4% can be considered in identifying individuals with high risk for future diabetes and this state of intermediate hyperglycaemia can be considered as prediabetes (Anonymous et al., 2012).

2.4 The pathophysiology of Pre-diabetes

Insulin resistance and β-cell failure represent the main pathophysiological defects in prediabetes which eventually leads to abnormal glucose levels (Abdul-Ghani MA et al., 2006). Subjects with prediabetes are mostly insulin resistant and have lost a substantial amount of their β-cell function but the location of resistance differs in IFG as opposed to IGT. Those individuals with isolated IGT have moderate to severe muscle insulin resistance and reduced hepatic insulin sensitivity but those with IFG have altered hepatic insulin resistance but normal muscle insulin sensitivity. Other distinguishing features to the mechanism of altered blood glucose metabolism involves a difference in their insulin secretion patterns. There is an altered late phase insulin secretion response to an IV glucose load in individuals with isolated IGT with a normal first phase insulin response. Whereas for individuals with isolated IFG there is a blunted first phase insulin secretion (Weyer C et al., 1999). Additionally, the Glucagon-like-peptide levels are reduced in individuals with both IFG and IGT as opposed to those with isolated IFG or IGT (Zhang F et., 2012).

2.5 Diagnosis of Diabetes Mellitus:

Diabetes mellitus can be diagnosed in multiple ways. Each way usually needs to be repeated a second time to confirm diabetes.

2.5.1 HbA1C**:** The Glycosylated Hemoglobin in short HbA1C or simply A1C refers to the average blood sugar of last two to three months. Diabetes is diagnosed if the A1C of greater than or equal to 6.5% (Anonymous et al., 2022). It is shown in % .

Table 1: Diagnosis of DM regarding HbA1C (Adapted from ADA, 2022)

Result	HbA1C
Normal	<5.7%
Pre-diabetes	5.7-6.4%

Diabetes	≥6.5%

2.5.2 Fasting Plasma Glucose (FPG)**:**By fasting plasma glucose level, a person can be labeled as a diabetic, IFG or normal. A person with normal glucose or IFG , if subjected to OGTT, may be found to be diabetic or IGT.

Table 2: Diagnosis of DM regarding Fasting Plasma glucose (Adapted from ADA 2022)

Result	Fasting Plasma Glucose(FPG)
Normal	<100mg/dl
Pre-diabetes	100-125 mg/dl
Diabetes	≥126mg/dl

2.5.3 Oral Glucose Tolerance Test (OGTT)**:** Plasma glucose level is determined by fasting and 2 hours after 75 grams of oral glucose drink. It classifies a person as a diabetic, IGT or IFG.

Table 3: Diagnosis of DM regarding Oral Tolerance Test (OGTT) (Adapted from ADA 2022)

Result	Oral Glucose Tolerance Test (OGTT)
Normal	<140mg/dl
Pre-diabetes	140-199 mg/dl
Diabetes	≥200mg/dl

2.5.4 Random Plasma Glucose (RPG)**:** No preparation is required for this procedure. Plasma glucose levels are estimated from a sample irrespective of the last meal. RPG, in presence of classical symptoms of hyperglycaemia or hyperglycaemic crisis with a blood sugar reading of ≥11.1, can confirm diabetes (Anonymous, et al., 2022).

2.6 Screening for prediabetes and type 2 diabetes in adults

Testing for prediabetes/type 2 diabetes in asymptomatic should be considered in adults of any age who are overweight/obese (BMI ≥23 kg/m^2 in Asians) and who have one or more of the following risk factors:

- First-degree relative with diabetes
- High-risk race/ethnicity, like Bangladeshi's
- History of CVD
- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dl and/or a triglyceride level >250 mg/dl
- Women with polycystic ovary syndrome (PCOS)
- Physical inactivity
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

For all other people (even without risk factors), testing should begin at the age of 35 years.

If results are normal, testing should be repeated at 1-3 year intervals, with consideration of more frequent testing depending on initial results and risk status. Patients with prediabetes (A1C ≥5.7%, IGT, or IFG) should be tested yearly. Women who were diagnosed with GDM should have lifelong testing at least every 1-3 years. Immediate testing is required in symptomatic cases (Anonymous et al., 2022).

Screening of patients for prediabetes could also implement the use of validated risk calculators such as Finnish Diabetes Risk Score (FINDRISK), or Canadian Diabetes Risk Assessment Questionnaire (CANRISK), Framingham risk score etc. (Anonymous et al., 2012).

Random plasma glucose, FPG, HbA1c, OGTT or Glucose Challenge tests etc. are the preferred methods for screening for prediabetes. The nature of the tests depend on clinical features and patient preferences (Tabak AG, et al., 2012).

It should also be noted that excessive screening may lead to over diagnosis, unnecessary investigations, treatment and adverse effects, psychosocial and economic costs. Hence, there is lack of clear clinical evidence to support screening subjects with low to moderate risk of diabetes. However, with a targeted approach for high risk patients, the screening costs could be reduced (Anonymous et al., 2012).

2.7 Complications of Pre-diabetes

Pre-diabetes is linked with an increased risk for developing both microvascular and macrovascular complications.

IGT can be an independent risk factor for future stroke which was evident in the **DUTCH TIA** study findings (Vermeer SE et al., 2006). Individuals with IGT The **DECODE** study were more prone to develop cardiovascular disease risk and all-cause mortality as per the findings of the DECODE study, but it was less evident for IFG. The Diabetes Prevention Program also showed that Diabetic retinopathy was also found to be more common in individuals with Pre-diabetes (Nathan MD, 2007). Many studies showed increased prevalence of polyneuropathy in isolated IGT compared with isolated IFG (Ziegler D et al., 2008). Several reports also showed an increased prevalence of early diabetic nephropathy in terms of microalbuminuria in IGT patients as compared to normoglycemic participants (16 vs 4%) (Curb JD et al., 1995). Finally, all complications of diabetes can occur in Pre-diabetes, and this is more evident in those patients with IGT than IFG.

2.8 Prevention of Prediabetes

2.8.1 Prevention of Prediabetes through Lifestyle Modifications

The Diabetes Prevention Program (DPP) (Knowler WC et al., 2009), the Finnish Diabetes Prevention Study (DPS) (Tuomilehto J et al., 2001), China Da Qing Diabetes Prevention Study (CDQDPS) (Li G et al., 2008) and the Indian Diabetes Prevention Program (IDPP-1) (Ramachandran A et al., 2006) all demonstrated that an exercise intervention of about 150 minute/week together, dietary intervention along with weight reduction from 5-7% during the period of the study could lead to significant reductions (29-58%) in the progression to T2DM from prediabetes.

2.8.2 Prevention of Prediabetes through Medications

Results from the DPP research (Knowler WC et al., 2009) and the IDDP (Ramachandran A et al., 2006) studies demonstrated a significant relative risk reduction (25-30%) in those individuals with prediabetes that were treated with metformin irrespective of lifestyle modifications. Other studies with α-glucosidase inhibitors (Acarbose (Chiasson JL et al., 2002) and Voglibose) (Kawamori R et al., 2009) also demonstrated remarkable reductions in the incidence of T2DM from prediabetes (25-40%) with a strikingly large proportion of the IGT individuals also returning to normal glucose tolerance by using acarbose. The ACT NOW study (DeFronzo RA et al., 2011) with pioglitazone also demonstrated similar results of conversion from IGT to normoglycaemia with 30-45 mg doses with findings

consistent with the previous studies with acarbose intervention (Chiasson JL et al., 2002).

2.9 Further implications for screening in developing countries.

We face a big dilemma in the developing nations because of the effects of diabetes related complications especially in the working age-groups. These countries do not have the infrastructure to manage the advanced stages of the disease and are ill-equipped with modern facilities or resources. However, there are strategies that can be easily implemented that can aid screening in these countries.

One such measure involves taking examples from cost-effective interventions used in developed countries to prevent diabetes and implementing them in screen-detected people of developing countries. However, it remains a great challenge to effectively implement these interventions, and the costs and benefits of diabetes screening in these settings are less well-known. Implementing screening policies in developing countries will require health systems strengthening, through creative funding and staff training.

For compelling and justified reasons screening for hyperglycaemia should be a policy priority in developing countries. This will help reorient health systems toward cost-saving prevention (Chowdhury SR et al., 2018).

2.10 Insulin Resistance

Insulin sensitivity results from the biological effects of insulin in its insulin-responsive tissues mainly the skeletal muscle, liver, and adipose tissue. Insulin resistance also termed as impaired insulin sensitivity is defined by reduced skeletal muscle glucose clearance, suppressed glucose production by the liver and reduced adipose tissue lipolysis.

The Hyperinsulinaemic-euglycaemic glucose clamp (HEGC) method is the gold standard procedure for measuring insulin resistance and insulin sensitivity (DeFronzo RA et al., 1979). The method relies on the constant interaction between the glucose concentrations and insulin secretion which disrupts their physiological feedback loop mechanism. Whole-body insulin sensitivity can then be assessed by continuous glucose infusion rates which are required to maintain a level of glycaemic status which is given as the M value (Andres R et al., 1962).

The HEGC clamp method is unfortunately time consuming, difficult to operate and requires a fair level of expertise. So, far more simpler tests that have been developed for assessing insulin sensitivity in epidemiological studies. These include the homeostasis model assessment (HOMA-IR) (Matthews DR et al., 1985) and the QUICK1 (Katz A et al. 2000') which are calculated from the fasting plasma glucose and C-peptide/Fasting Serum Insulin concentrations (Wallace TM et al., 2002). It has its limitations because it relies on the fact that the liver is responsible for contributing to the FPG and relies on expensive tests like fasting serum insulin and C-peptide levels for routine diagnosis (Ekberg K et al., 1999). Likewise, the glucose is thereby utilized up to 60% in non-insulin-dependent tissues, such as the brain, and to lesser extent in insulin-sensitive tissues, such as muscle and liver (Baron AD et al., 1985). Therefore, the insulin resistance derived from the fasting plasma glucose parameters do not correlate with the clamp-derived glucose disposal. Furthermore, it is not a valid measure of calculating insulin sensitivity when overt diabetes occurs which disrupts the physiological balance between circulating glucose and insulin concentrations (Malita FM et al. 2006), (Radziuk 2000).

2.10.1 Insulin Resistance and the Metabolic Syndrome

The Metabolic syndrome (MS) occurs as a cluster of metabolic and medical disorders. Among them obesity, glucose intolerance, dyslipidaemia and hypertension develop together. These constellations of defects cannot readily be explained to occur by chance.

In the ongoing debates about MS the key issue is whether this cluster of abnormalities arise from obesity or insulin resistance (IR). The lack of consensus on major underlying factors in the development of MS is the illustrated history of its different names e.g., plurimetabolic syndrome, syndrome X, Deadly quartet, Reaven's syndrome, insulin resistance syndrome, dysmetabolic syndrome, etc.

The International Diabetes Federation proposed a new definition of metabolic syndrome in 2006 (Alberti SG et al. 2006). Those involved in establishing the diagnosis of MS agreed that diabetes and insulin resistance had been over emphasized in previous definitions; and that the essential component is central obesity-measured by waist circumference. Ethnicity specific cut off points had been selected based on available data.

The new definition of IDF proposed that in order for a person to have metabolic syndrome they must fulfil the following criteria (Alberti SG et al. 2006):

1. Central Obesity (waist circumference according to ethnicity.
2. Plus, any of the two following criteria:
    - Raised TG >150 mg/dl
    - Reduced HDL (Male <40 mg/dl and Female <50 mg/dl)
    - Raised BP: Systolic >130 mm of Hg and Diastolic > 85 mm of Hg
    - Raised FPG >5.6 mmol/l (100mg/dl)

It should also be noted that BMI >30kg/m2 is also acceptable as central obesity and IGT is also acceptable as raised plasma glucose.

So, the metabolic syndrome (MS) is the constellation of metabolic abnormalities which include central obesity, atherogenic dyslipidaemia, hypertension, hyperglycaemia. The MS is associated with a fivefold risk for type 2 DM and two-to-three-fold risk for CVD.

MS is now considered as one of the principle public health issues of the 21st century and is now considered a global health challenge.

There are also additional metabolic criteria for research which are recommended by the IDF Group. These include:

1. Abnormal body fat distribution measurement.
2. Other atherogenic lipids (Apo-B, small LDL particles)
3. Insulin Resistance (other than FPG)
4. Vascular abnormality (Beyond high BP, endothelial dysfunction)
5. Proinflammatory state (CRP, TNF, IL-6)
6. Prothrombotic state (PAI-1, Fibrinogen)
7. Hormonal Factors (Pituitary Adrenal Axis)
8. Generic factors (Alberti SG et al. 2006).

2.10.2 Insulin Resistance at the level of Skeletal Muscle

The main mechanism underlying insulin resistance in individuals with type 2 diabetes is a drastic reduction (60%) in the insulin-stimulated glycogen synthesis. Furthermore, after ingestion of meals the muscle glycogen synthesis increase was 30% lower in diabetic patients despite double the concentration of serum insulin. Hence, all the abnormalities related to muscle insulin resistance in T2DM patients could be

attributed to an abnormal insulin-stimulated glucose transport via glucose transporter4 (GLUT4) (Shulman GI et al., 1990).

There are also other abnormalities that contribute to human muscle insulin resistance which could be lipid-induced that result from the reduced muscle insulin-stimulated glucose transport resulting in impaired glucose phosphorylation and reduced insulin-stimulated glycogen synthesis.

Furthermore, intramyocellular TAGs predict muscle and liver insulin resistance far better than circulating plasma FFAs. Moreover, excess dietary could also contribute to muscle insulin resistance and type 2 diabetes can also be predicted by the circulating branched-chain amino acids.

Certain other metabolic factors can contribute to muscle insulin resistance other than ageing such as hyperglycaemia and dyslipidaemia by impairing mitochondrial function (Cline GW et al., 1999).

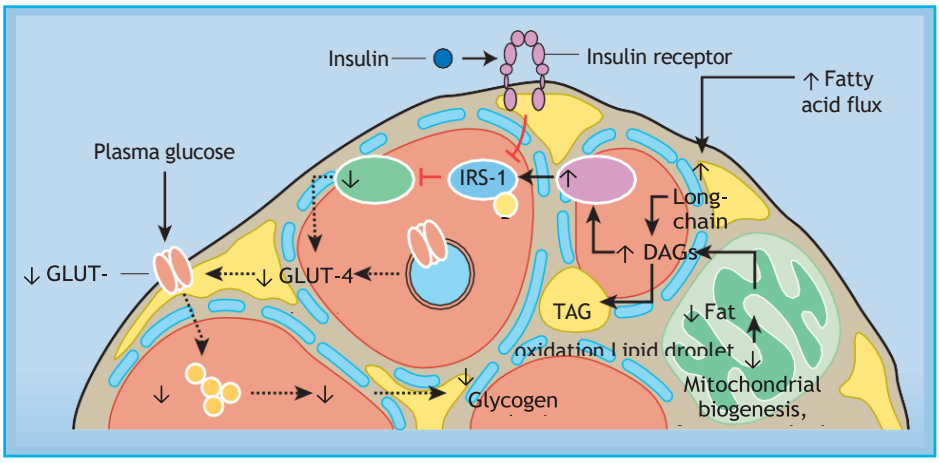


Figure 1: Cellular mechanism of insulin resistance in human skeletal muscle (adapted from Shuman et al., 2014)

An increase in the fatty acid influx causes a concomitant increase in the intracellular long-chain fatty acid (CoA) pool which in turn fuels the oxidation of mitochondria that or serves to synthesize diacylglycerols (DAGs) for storage as triglyceride (TAG) lipid droplets. As a result there is an increase in the intracellular DAG content. The DAGs then promotes the activation of Protein Kinase C isoforms (nPKC). Membrane translocation of PKC isoforms then leads to increase in the serine phosphorylation of insulin receptor substrate 1 (IRS-1) and in turn binds and activates the phosphatidylinositol 3-kinase (PI3K). This ultimately leads to a reduction in the recruitment of GLUT-4 units to the membrane with impaired insulin-stimulated glucose uptake and phosphorylation to glucose-6-phosphate (G-6-P) and ultimately decreased insulin-stimulated glycogen synthesis.

2.10.3 Insulin Resistance at the level of the liver

The liver has a dual role in blood glucose homeostasis. It can regulate both the fasting and postprandial blood glucose levels as it is both a glucose-storing and a glucose-producing organ as well. After a meal is ingested, the liver stores the excess glucose

in the form of glycogen and suppresses the glucose production (DeFronzo RA et al., 2004).

In T2DM individuals with insulin-resistance, there is an impaired suppression of glucose production because of excessive postprandial hyperglycaemia in coexistence with 45% lower hepatic glycogen production in contrast to healthy individuals.

Data from animal models show that lipid intermediates like DAGs inhibit hepatic insulin signaling and stimulate hepatic triglyceride accumulation like that of skeletal muscle lipid-mediated insulin resistance (Krssak M et al., 2004).

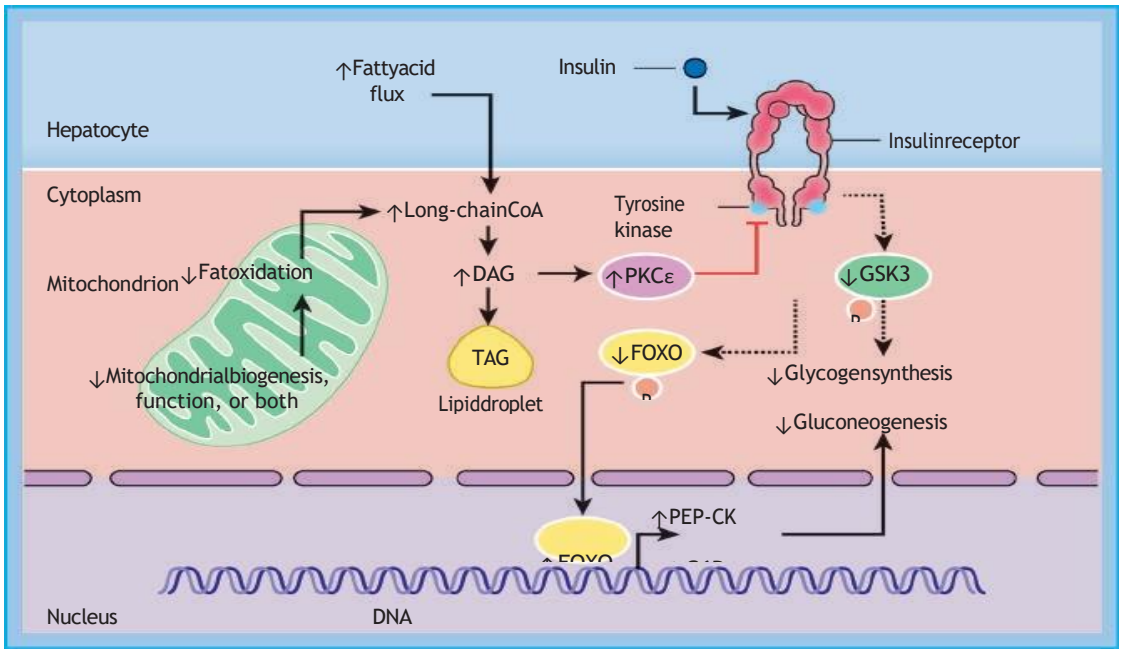


Figure 2: Cellular mechanism of insulin resistance in liver (Adapted from Shuman et al., 2014)

An imbalance of intrahepatocellular fluxes gives rise to hepatocellular diacylglyerols (DAGs), particularly when DAG synthesis, from both fatty acid re-esterification and de novo lipogenesis, exceeds the rates of mitochondrial oxidation of long-chain fatty acyl-coenzyme A (CoA) and/or the rates of DAG incorporation as triglycerides (TAGs) into lipid droplets. This activates the epsilon isoform of protein kinase C (PKCε), which likely phosphorylates the insulin receptor tyrosine kinase. In turn, phosphorylation of glycogen synthase kinase 3 (GSK3) phosphorylation increases, while that of forkhead box subgroup O (FOXO) decreases. This results in inhibition of glycogen synthase activity and thereby lower insulin-stimulated glycogen storage and in FOXO-mediated gene transcription of the gluconeogenic enzymes (e.g. phosphoenolpyruvate carboxykinase [PEP-CK] and G6P), with decreased insulin suppression of hepatic gluconeogenesis.

2.10.4 Insulin Resistance at the level of the adipose tissue

In the adipose tissue, there is an increased plasma concentration of TAGs and FFAs and in case of insulin resistance and especially T2DM there is decreased sensitivity to insulin and it's corresponding action on lipolysis (Groop LC et al. 1989).

The liver and muscle are subjected to lipid-mediated effects because of the changes to its homeostasis on insulin sensitivity. A state of "sub-clinical inflammation" arises from the adipose tissue because of obesity and metabolic syndrome which leads to an imbalance of adipocytokine secretion which have anti-inflammatory and insulin-sensitizing entities such as adiponectin and proinflammatory cytokines like leptin, TNF-α and IL-6 amongst others. These adipocytokines could cause insulin resistance in the liver and muscle by activating JNK1 which is involved in chronic insulin resistance. The activation of inflammatory cytokines could also result in obesity-induced insulin resistance and could also contribute to chronic hyperglycaemia in T2DM patients (Shoelson SE et al., 2006).

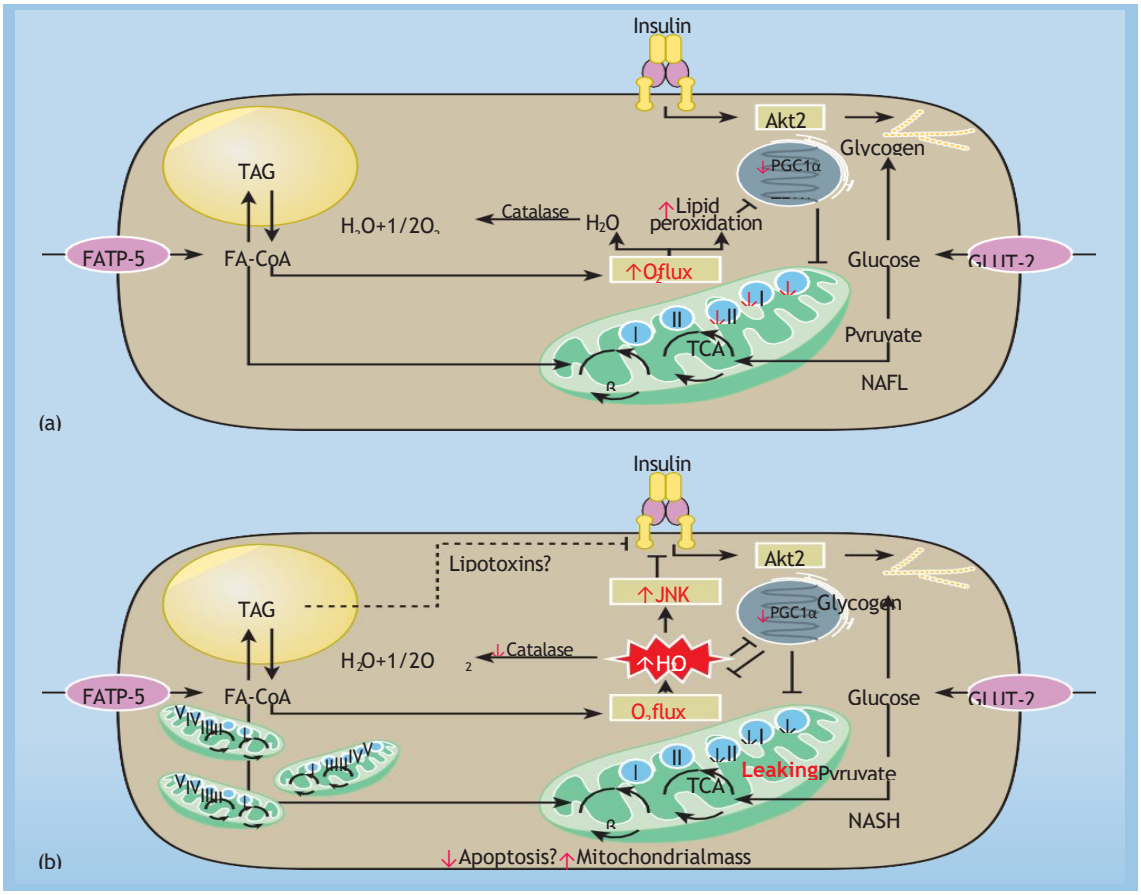


Figure 3: Cellular mechanism of insulin resistance in adipose tissue (Adapted from Koliaki et al., 2015)

Hypothesis of adaptation of hepatic energy metabolism in the pathogenesis of non-alcoholic fatty liver disease and progression of hepatic insulin resistance. (a) In states of obesity, increased fatty acid delivery upregulates hepatic mitochondrial oxidative capacity, which prevents excessive storage of triacylglycerols (TAGs) but promotes the accumulation of reactive oxygen species and lipid peroxides, which are scavenged by hepatic catalase activity. (b) During the development of non-alcoholic fatty liver disease (NAFLD), the efficiency of mitochondrial coupling fails, which accelerates the generation of hydrogen peroxide (H2O2) in the face of decreasing catalase activity. Finally, oxidative stress decreases mitochondrial biogenesis, but increases leakage of mitochondria and activates c-Jun N-terminal kinase (JNK), which drives cellular inflammation and progression to steatohepatitis (NASH).

2.11 Triglycerides and CVD Risk

Triglycerides, also called triacylglycerols, are formed as result of a single combination of glycerol and fatty acids in heterogenous fashion and are measured collectively. Triglycerides have both exogenous and endogenous sources. Endogenous sources are collected from dietary fat and are carried in chylomicrons which are produced primarily in the gut and exogenous sources are carried in very low-density particles which are produced in the liver. There is a complex mechanism that underlies the explanation behind the elevated triglyceride levels in diabetic patients. These mechanisms could be attributed to defective insulin action and hyperglycemia which cause an apparent and distinctive change in plasma lipoproteins in individuals with diabetes as opposed to the normal population. Subsequently, obesity and insulin resistance could also contribute to secondary abnormalities of lipid metabolism in individuals with T2DM.

In T2DM, primarily there is an increase production of VLDL particles and its ApoB counterpart in the liver secondary to elevated free fatty acid influx to the liver because of enhanced adipose tissue lipolysis in the background of insulin resistance and/or insulin deficiency. Consequently, Triglycerides have also been stated as an independent risk factor for Cardiovascular disease in several meta-analyses. On the contrary, high serum triglyceride levels are associated with lipid metabolism abnormalities and coincide with other CVD risk factors like obesity, insulin resistance, diabetes, low levels of HDL-C it is therefore difficult to establish them as independent CVD risk factors and so the studies can be conflicting and bemusing at times. Even so, some causes of hypertriglyceridemia have little or no effect on atherosclerotic cardiovascular disease hence making it difficult to prove that there is any direct link between hypertriglyceridemia and CVD (Sarwar N et al., 2007).

2.12 Common Soil Hypothesis

In 1995 Michael P. Stern mentioned the term **“common soil hypothesis”** which has since gained momentum recently in identifying a common link between T2DM and CVD and studies show that elevated blood pressure, smoking, elevated total triglycerides, and ALT concentrations are causal risk factors for CVD and T2D. Thereby, demonstrating that both these chronic conditions have similar genetic and environmental antecedents (Stern MP, 1995).

Materials and Methods

Chapter III: Methods and Materials

3.1 Study area

People's Republic of Bangladesh is a highly populated country situated in the south East Asia with about 170 million populations. In Bangladesh, Chattogram is the second largest city. It is situated in the south-east part of the country at the bank of the river Karnaphully. The population of the city is around 6 million. A nationwide survey was done in 2011 on prediabetic patients in Chittagong and it showed an age-adjusted prevalence of 29.2% which was the highest in the whole of Bangladesh (Akter S et al., 2014), hence this city was chosen as the study area owing to its high vulnerability for prediabetes.

3.2 Study site

Chittagong Diabetic General Hospital, Khulshi, Chattogram

3.3 Study design

The study was a descriptive/observational type of case-control study that was conducted in selected non-government diabetes multi-specialty hospital of Chattogram city named Chittagong Diabetic General Hospital.

3.4 Study population

All individuals attending the diabetes, endocrinology, and metabolism outpatient department of Chittagong Diabetic General Hospital during the time of this study is considered as the study population.

3.5 Study period

Data was collected for this study over a period of one year from October 2021 till end of September 2022.

3.6 Sampling method

Purposive sampling technique was used to collect the study sample. Patients who agreed to be enrolled in the study were collected consecutively until the targeted sample size was completed.

3.7 Procedure for calculating sample size.

During the 1 year study period, all patients who came to the diabetes, endocrinology, and metabolism outpatient department of outdoor department were approached and a total of 200 prediabetes and the corresponding age and sex-matched normoglycemic individuals gave their consent and agreed to be enrolled in our study.

3.8 Demographic data

Demographic data like age, sex, occupation, educational status, physical activity levels, socioeconomic status, dependency, personal habits (smoking, chewing tobacco), past medical history, symptoms of DM and dietary history were recorded with the structured questionnaire.

3.9 Anthropometric Measurements

- BMI was derived from the mass (weight) divided by the square of the height of the patient and was expressed in kg/m^2, whereby mass is measured in kilograms and height in meters respectively. BMI was calculated using the following formula:

  BMI = $\frac{\text{mass (kg)}}{\text{height (m}^2\text{)}}$

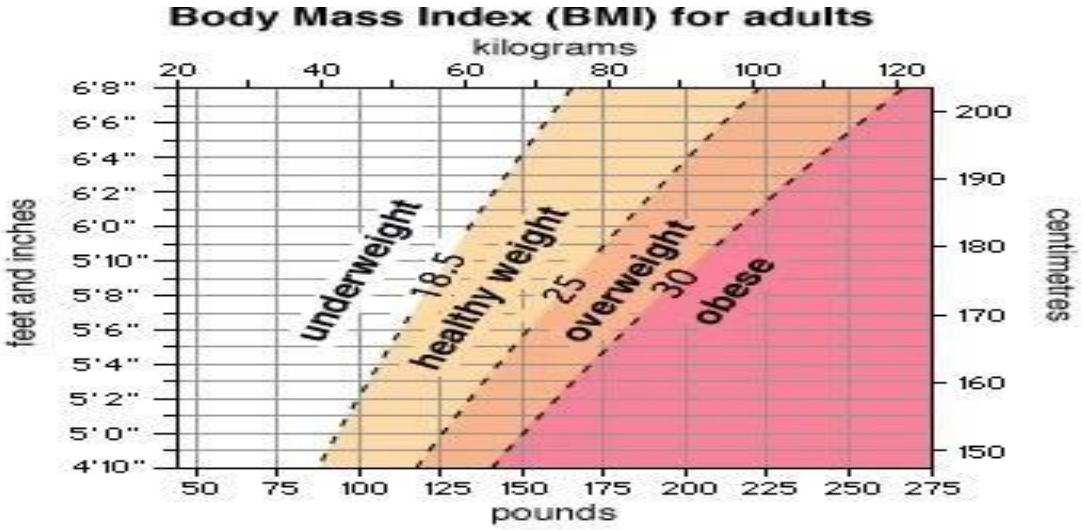


Figure 4: BMI chart for adults (Adapted from Textbook of Diabetes 5th Edition[65])

Category of the individual according to BMI (kg/m2):

1. Underweight : <18.5
2. Normal range : 18.5 – 24.9
3. Overweight (Pre-obese): 25.0 – 29.9
4. Obese (Class I): >30.0

The Waist Circumference was measured to the nearest 0.1 cm midpoint between the iliac crest and costal margin at the end of expiration.

3.10 Measurements of Biochemical parameters

Blood samples were collected from venous blood samples after an overnight fasting for 8-10 hours as per standard procedure. Fasting triglyceride levels were analyzed by a fully automated biochemical analyzer. Fasting plasma glucose was determined by the glucose oxidase and peroxidase method. HbA1c was estimated by High Performance Lipid Chromatography (HPLC). Fasting Triglycerides were assessed by enzymatic method and corrected for endogenous glycerol. Fasting plasma insulin was determined by direct chemiluminescent technology.

- **The Triglyceride Glucose Index (TyG) index** was derived from the following standard formula:
  ln [fasting TG (mg/dL) × FPG (mg/dL)/2] (Selvi NMK et al., 2021)
- **Insulin resistance** was measured by using the following formula:
  [HOMA-IR=fasting insulin (µIU/mL) *fasting glucose (mmol/L)/22.5]
  (Selvi NMK et al., 2021)

3.11 Inclusion and exclusion criteria

Inclusion criteria

- Diagnosed case of prediabetes according to the International standard by American Diabetic Association (ADA) (Anonymous et al., 2022).
- Normoglycemic patients.
- Provided written inform consent in the selected area in the Questionnaire.

Exclusion criteria

- Participants suffering from diabetes,
- Cirrhosis of the liver, HIV, chronic renal, pancreatic, or other severe illness,
- Female subjects who are pregnant, breastfeeding or planning a pregnancy, and

- Patients who are on steroids/nicotinic acid or other medications likely to cause dysglycemia.
- Patients who did not give consent for the study.

3.12 Ethical implications

Prior to collecting data, written permission was obtained from the director of the specified hospital. When approaching the study participants, a written informed consent was obtained from all participants before initiating their interview. The interview was conducted in a private room with only the interviewer and the respondent in the room. All collected data was kept in a secured place under lock and key. On data analysis in SPSS, all patient's names were replaced by serial numbers to protect identity. Hence, confidentiality was maintained.

3.13 Data collection tools

- Structured questionnaire.
- Physician's prescription of respondents.

3.14 Data collection procedure

All patients attending the diabetes, endocrinology and metabolism outpatient department during the study period were approached for this study. After obtaining consent, they were interviewed face-to face using a pre-tested semi- structured questionnaire. The results were then collected and compiled on a Microsoft excel worksheet.

3.15 Data analysis

The results were initially checked for mistakes. Completed questionnaires with missing or confusing responses were excluded. The compiled data was then transferred to a data analyzing statistical software SPSS version 26 created by International Business Machines (IBM). The results were presented as tables and charts and documented as mean±SD. Results are expressed as mean±SD. Difference in means between the groups was evaluated by independent t test. The Receiver Operating Characteristic (ROC) curve was plotted based on the sensitivity and specificity for HbA1c and TyG indexes. Pearson correlation analysis was done to assess the correlation between TyG index and HOMA-IR with weight, BMI, waist

circumference and waist-to-height ratio. A p- value of less than 0.05 was considered significant and a p value of less than 0.01 was considered highly significant.

Results

Chapter IV: Results

The present study was conducted at Chattogram district and data was collected over a period of 1year (September 2021- October 2022) from Chittagong Diabetic General Hospital, a Diabetes predominant referral based multi-specialty hospital which is located within the district. A total of 200 individuals with prediabetes (100) and their corresponding sex and age-matched normoglycaemic controls (100) were enrolled in the study. Amongst the 100 individuals with prediabetes, there were 51 males and 49 females that were enrolled in the study with the mean age being 47.23± 9.52 years. In comparison, the normoglycaemic controls consisted of equal no of males and females similar to their prediabetes counterparts and their mean age was 45.76 ± 8.9 years. In those individuals with prediabetes (n=100), 16% of the patients had impaired fasting glucose (IFG), 15% had impaired glucose tolerance and the remaining 69% had both IFG and IGT correspondingly.

4.1 The overall socio demographic, life style behavior and general health information of the individuals:

For individuals with prediabetes the most important information regarding the complications and associated factors are the analysis of their socio-demographic status, life style behavior and general health characteristics. These are being discussed below.

4.1.1 Sociodemographic status of the respondents

4.1.1.1 Occupational status of the respondents

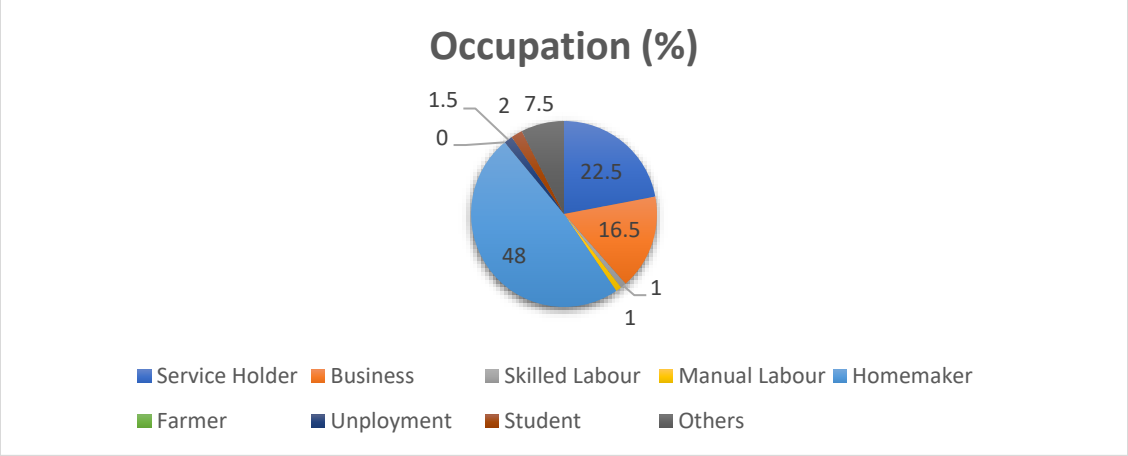


Figure 5: Occupational status of the respondents

Out of the 200 respondents, 97 (48%) were homemakers, 44 (22.5%) were service holders, 33 (16.5%) had their own private businesses, 15 (7.5%) were others, 4 (2%) were postgraduate students, 3 (1.5%) were unemployment, 2 (1%) were skilled and 2 (1%) were manual laborers and none were farmers (Fig 5).

4.1.1.2 Educational status of the respondents

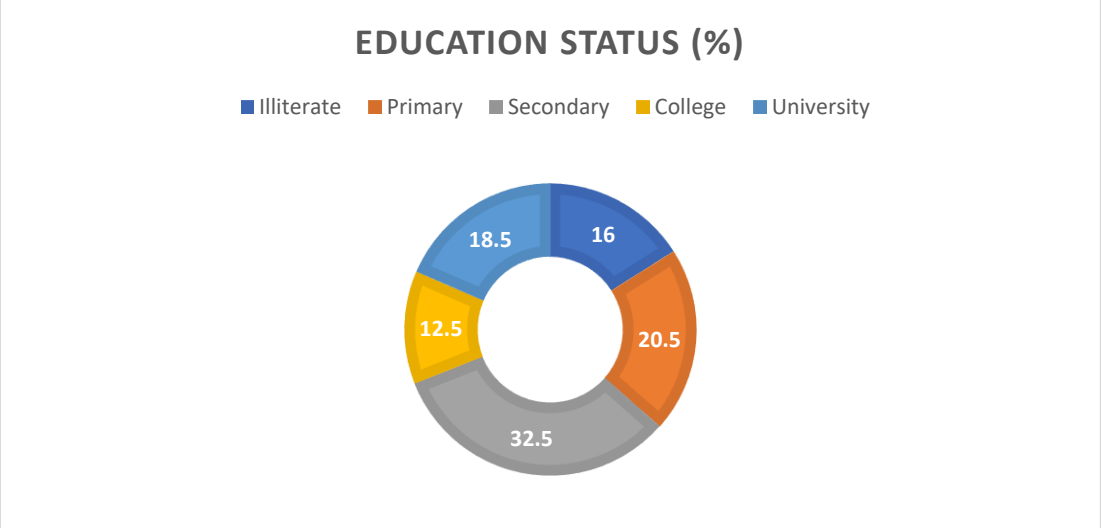


Figure 6 Educational status of the respondents

Out of the 200 respondents, 65 individuals (32.5%) had completed their secondary education, 41 (20.5%) had completed their primary education, 37 (18.5%) had completed their graduation from university or were enrolled in postgraduate studies, 32 (16%) were illiterate and 25 (12.5%) had completed their college education (Fig 6).

4.2 Personal History of the respondents

4.2.1 Economic Status of the respondents:

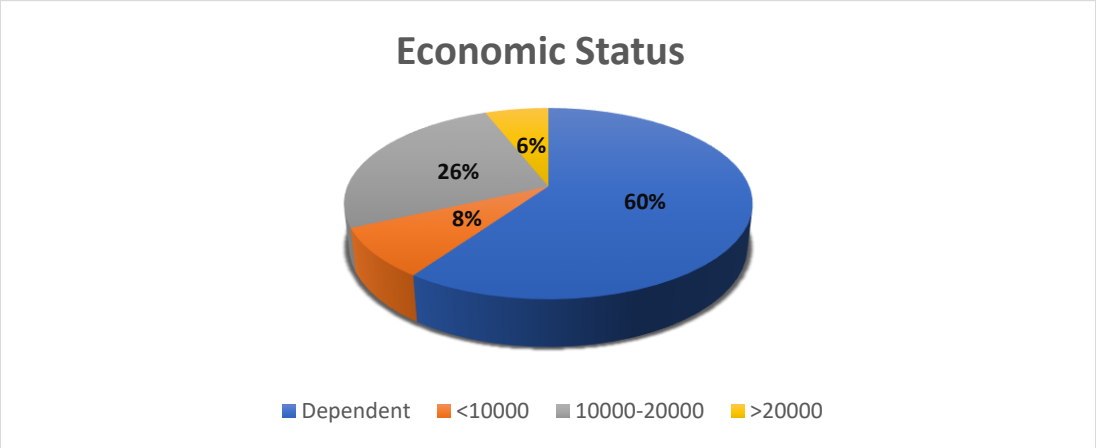


Figure 7: Economic status of the individuals

Out of the 200 respondents, a vast majority of them 120 (60%) were dependent, followed by 52 (26%) that were earning in the 10000-20000 Tk range, 16 (8%) were earning in the <10000 Tk range and 12 (6%) were earning in the >20000 Tk range (Fig 7).

4.2.2 Family History of the respondents

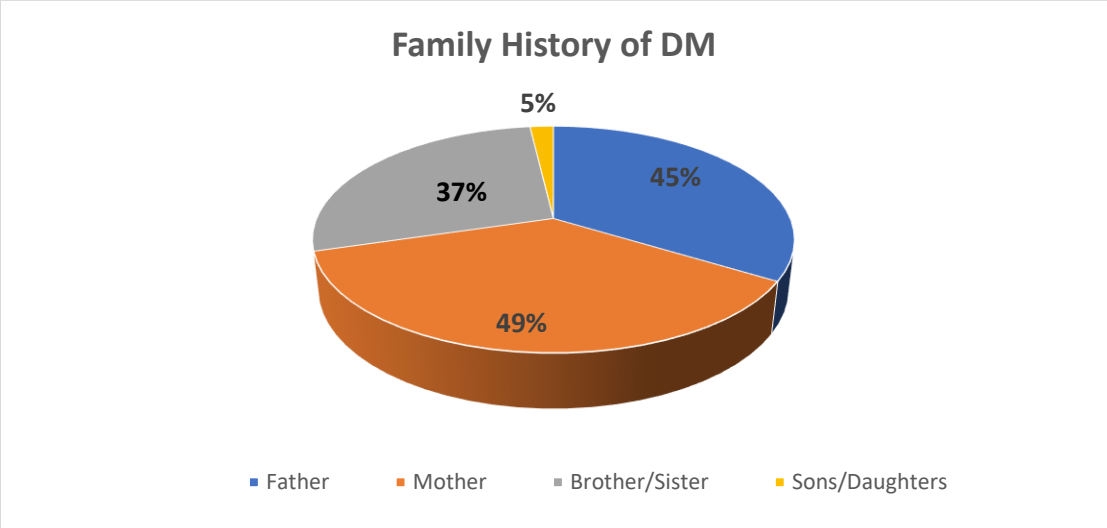


Figure 8: Family history of the respondents

Out of the 200 respondents, 49% had their fathers suffering from DM, followed by 45% of DM amongst their mothers, 37% amongst their siblings (brothers/sisters) and 5% amongst their children (sons/daughters). The distribution of DM were similar among their parents than their siblings and offspring.

4.3 Lifestyle status of the respondents

4.3.1 Physical activity of the respondents:

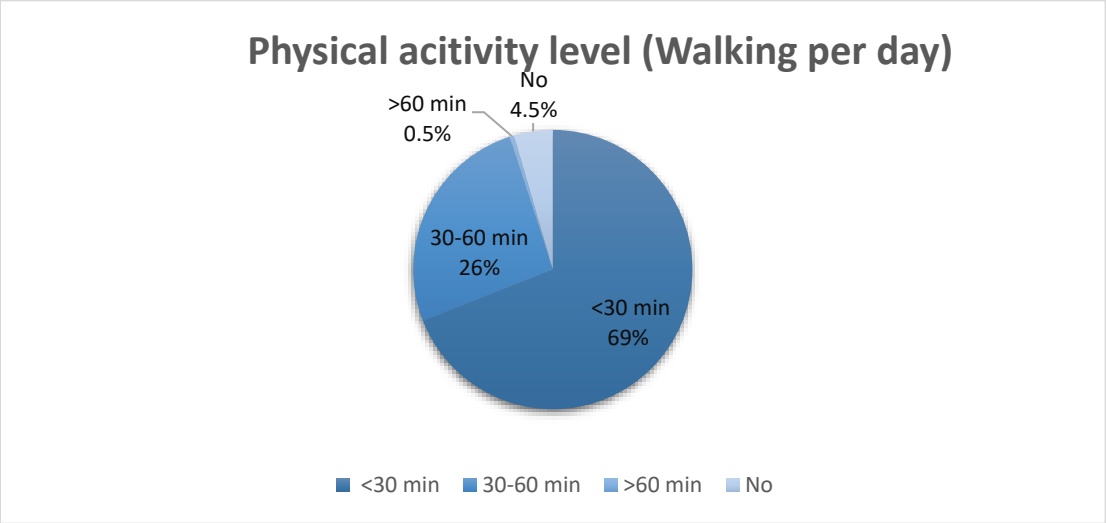


Figure 9: Physical activity of the respondents

Out of the 200 respondents, 138 (69%) individuals were engaged in <30 mins of walking per day, 52 individuals were engaged in 30-60 mins of walking per day, 9 (5%) individuals had no physical activity, and 1 (0.5%) individual was involved in >60 mins of walking per day (Fig 9).

4.3.2 Personal habits of the respondents

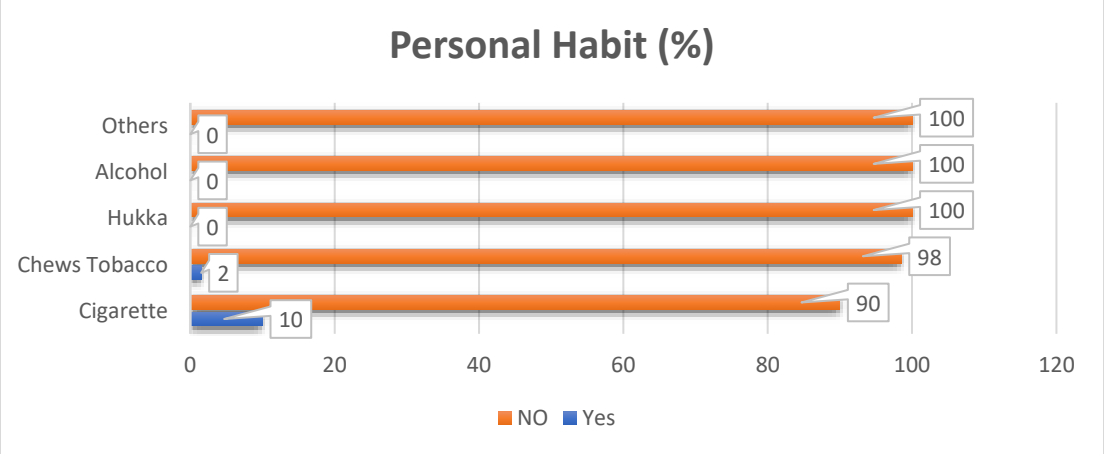


Figure 10: Personal habits of the respondents

Out of the 200 respondents, a vast majority 188 (94%) did not indulge in any addictions and only 10 (5%) individuals were cigarette smokers and 2 (1%) were consuming chewed tobacco while none of the respondents consumed any alcohol, hukka or any other drugs (Fig 10).

4.3.3 Dietary History (Green Vegetables and Fruits Consumption):

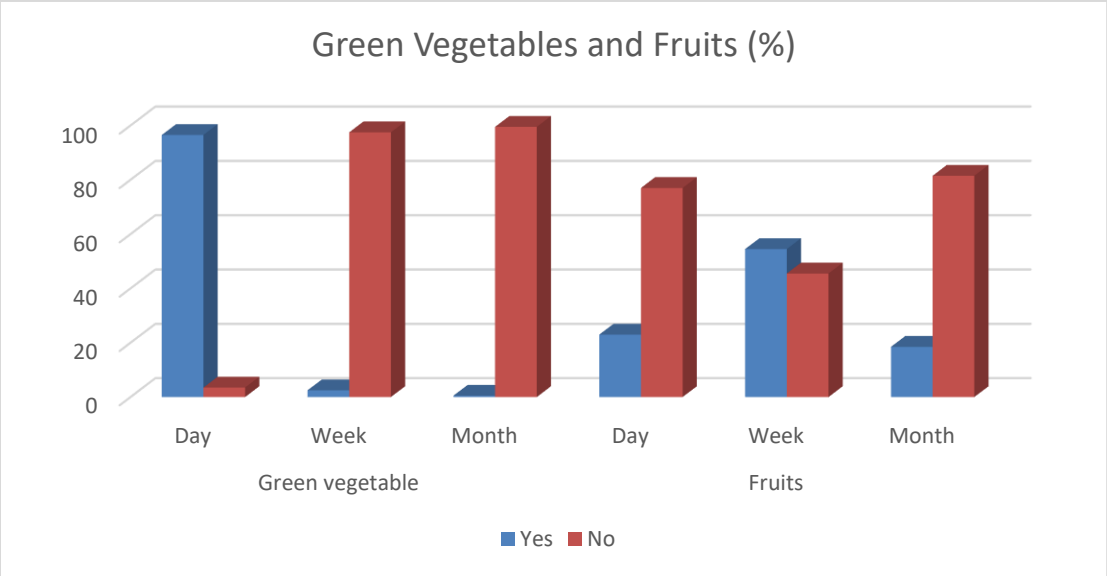


Fig 11: Dietary history of the respondents

Out of the 200 respondents, 193 (96.5%) consumed green vegetables at least once every day while 5 (2.5%) individuals consumed at least once every week and 2 (1%) consumed at least once every month. On the contrary only 49 (24.5%) individuals consumed fruits at least once every day, whereas 112 (56%) consumed at least once every week and 39 (19.5%) consumed at least once every month (Fig 11).

4.4 General Health of the respondents

4.4.1 Presenting Symptoms of DM on diagnosis:

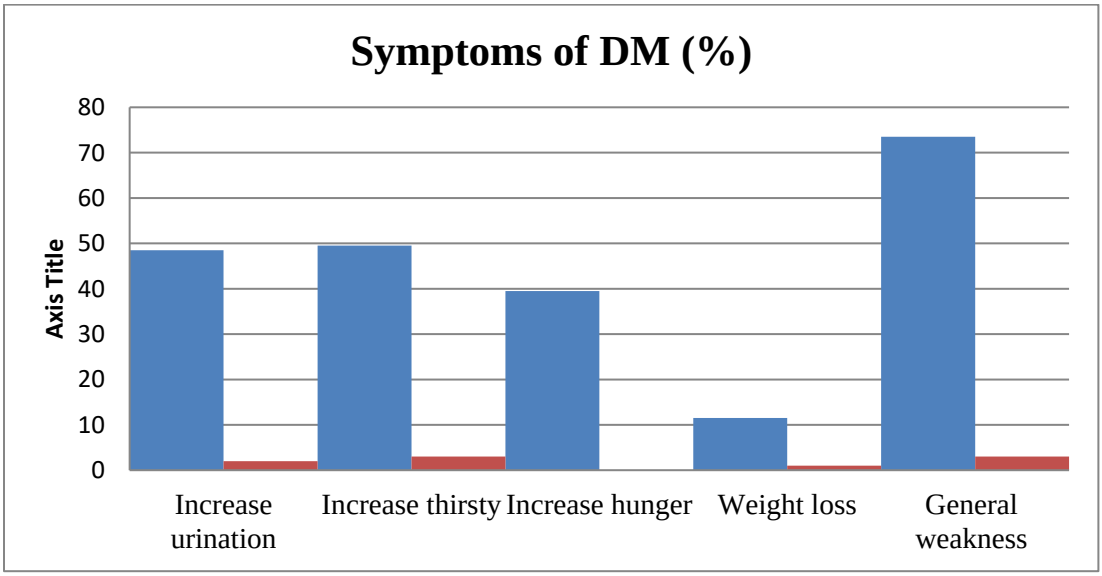


Figure 12: Presenting symptoms of DM on diagnosis.

Out of the 200 respondents, 48.5% of the individuals presented with increased urination (polyuria), 49.5% with increased thirst (polydipsia), 39.5% with increased hunger (polyphagia), 11.5% with weight loss and 73.5% with generalized weakness in their primary complaints for suspecting DM as a diagnosis for their condition (Fig 12).

4.4.2 Past Medical History:

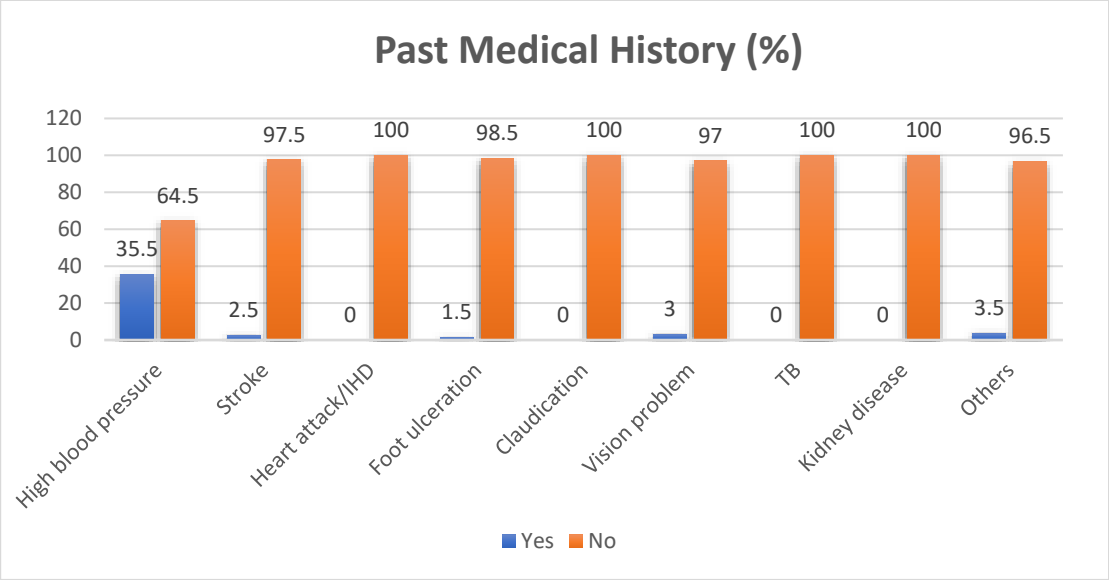


Figure 13 Past medical history of the respondents

Out of the 200 respondents,35.5% had hypertension, 3.5% had other conditions, 3% had vison problems, 2.5% had stroke, 1.5% had foot ulcers and none had any history of heart attack, intermittent claudication, TB or Kidney Disease (Fig 13).

4.5 Comparison of anthropometric parameters between cases and controls

Table 4: Anthropometric parameters between cases and controls groups

Anthropometric parameters	Cases (n=100)	Control (n=100)	Total	P value
Weight (in Kg) Mean ± SD	76.25 ± 12.45	66.8 ± 17.45	71.65 ± 15.67	<0.01
Height (in cm) Mean ± SD	163.57 ± 9.62	164.83 ± 12.71	163.09 ± 11.13	0.79
Body mass index (kg/m^2) Mean ± SD	28.69 ± 4.05	25.36 ± 4.08	26.76 ± 4.52	<0.01
Waist Circumference (cm) Mean ± SD	99.36 ± 10.67	90.55 ± 11.03	94.63 ± 11.38	<0.001

The mean weight (76.25 ± 12.45 vs 66.8 ± 17.45), Body Mass index (28.69 ± 4.05 vs 25.36± 4.08) was significantly higher in the cases vs the controls and the waist circumference (99.36 ± 10.67 vs 90.55 ± 11.03) was highly significantly in the prediabetes patients as compared to their normoglycemic controls signifying that obesity could be a risk factor for prediabetes. There was, however, no significant difference in the heights of the individuals (163.57 ± 9.62 vs 164.83 ± 12.71) in the prediabetes vs their normoglycaemic counterparts (Table 4).

4.6 Comparison of the laboratory parameters between cases and controls

Table 5: Laboratory parameters between cases and controls groups

Biochemical Parameters	**Cases (n=100)**	**Control (n=100)**	**P value**
Fasting Plasma Glucose (mg/dl) Mean ± SD	113.52 ± 9.67	88.03 ± 8.86	<0.001
Oral Glucose Tolerance (mg/dl) Mean ± SD	152.86 ± 18.8	117.15 ± 13.29	<0.001
Fasting Serum triglycerides (mg/dl) Mean ± SD	180.01 ± 38.18	134.98 ± 37.52	<0.001
Fasting Serum insulin levels (micro U/ml) Mean ± SD	8.542 ± 3.52	4.93 ± 2.68	<0.001
HbA1C (%) Mean ± SD	5.93 ± 0.25	5.36 ± 0.42	<0.001
Triglyceride glucose index (TyG) Mean ± SD	4.863 ± 0.142	4.672 ± 0.183	<0.001
HOMA-IR Mean ± SD	2.468 ± 1.062	1.05 ± 0.587	<0.001

In the analysis of the laboratory parameters, we found a highly statistically significant difference between the Mean Fasting Plasma Glucose (113.52 ± 9.67 vs 88.03 ± 8.86), Oral Glucose tolerance Test (152.86 ± 18.8 vs 117.15 ± 13.29) , Fasting serum triglycerides (180.01 ± 38.18 vs 134.98 ± 37.52), Fasting Serum insulin levels (8.542 ± 3.52 vs 4.93 ± 2.68), HbA1c (5.93 ± 0.25 vs 5.36 ± 0.42), Triglyceride Glucose Index (4.863 ± 0.142 vs 4.672 ± 0.183) and HOMA-IR levels (2.468 ± 1.062 vs 1.05 ± 0.587) with a p value of <0.001 suggesting that all metabolic parameters were raised in the prediabetes individuals as compared to their normoglycaemic controls (Table 5).

4.7 Comparison of Area Under Curve (AUC) of HbA1C and TyG index for the diagnosis of prediabetes

Table 6: Area under Curve (AUC) of HbA1c and TyG index for the diagnosis of prediabetes

Parameter	AUC	P value	Cut-off point	Sensitivity	Specificity	Youden's Index
HbA1C	0.923	<0.001	>5.53	0.912	0.820	0.73
TyG Index	0.874	<0.001	>4.762	0.845	0.805	0.66

The Area under the curve (AUC) demonstrates a higher ROC AUC score for HbA1c (0.923) as compared to the TyG Index (0.874) for diagnosing prediabetes (Table 6). These values were further validated with the Youden's index which further demonstrates the afore-mentioned variations between HbA1c and TyG index (0.73 vs 0.66), but the differences were not statistically significant with a p-value of 0.062. The cut-off point for HbA1c was >5.53 with a maximum sensitivity of 0.912 and sensitivity of 0.820 for the diagnosis of prediabetes while the cut-off point for TyG Index was >4.762 with a maximum sensitivity of 0.845 and specificity of 0.805 respectively (Figure 14). Both these differences in the cut-off point sensitivities and specificities were highly statistically significant for the diagnosis of prediabetes and further demonstrates that TyG index is comparable to HbA1C for the diagnosis of prediabetes (Table 6).

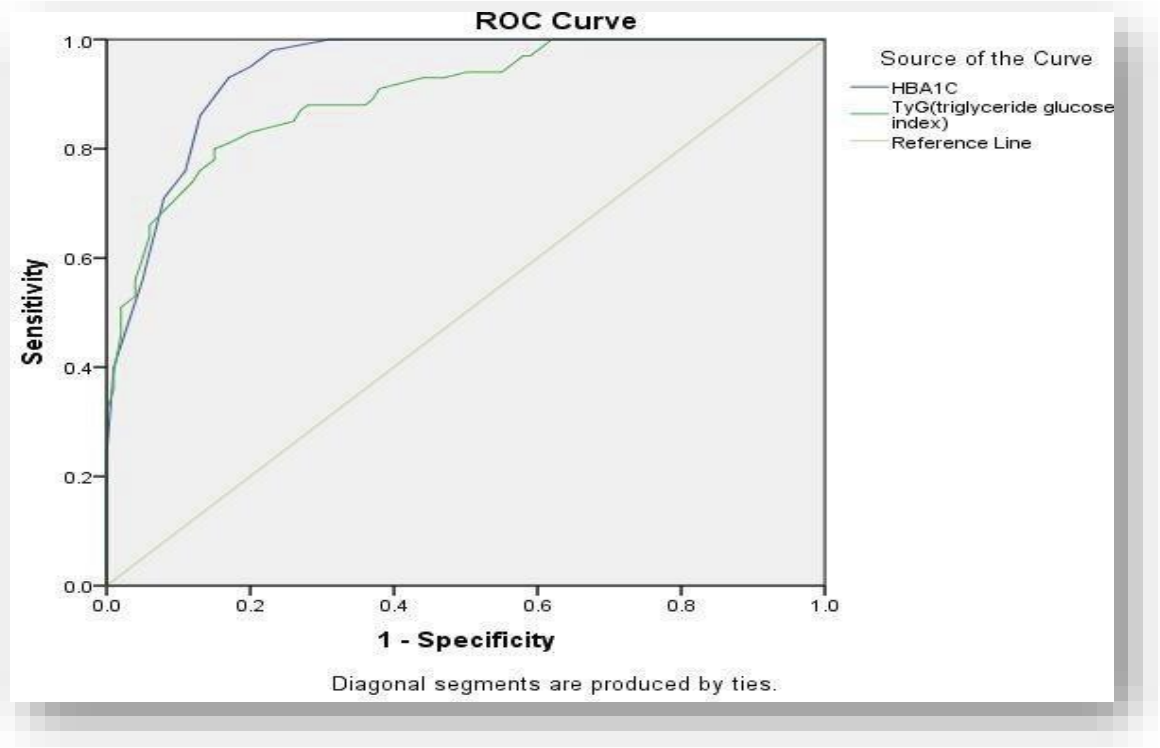


Figure 14: Comparison of ROC (receiver operating characteristic curve) curves of HbA1C and Triglyceride glucose index for the diagnosis of Prediabetes

4.8 Correlation of various Anthropometric measurements with TyG index and HOMA-IR

Table 7: Correlation of various anthropometric measurements with TyG index and HOMA

Parameter	Triglyceride Glucose (TyG) Index	HOMA-IR
Weight	0.186*	0.154**
Body Mass Index	0.421*	0.372*
Waist Circumference	0.286*	0.253*
Waist to height ratio	0.392*	0.333*

*P<0.01
**P<0.05

The Pearson correlation coefficients between the various anthropometric measurements related to insulin resistance with TyG Index and HOMA-IR demonstrates a highly significant difference in weight (0.186 vs 01.54) in favor of TyG Index with a p-value of <0.01 and a significant difference in Body Mass Index (0.421 vs 0.372), Waist Circumference (0.286 vs 0.253) and Waist to height Ratio (0.392 vs 0.333) which further demonstrates that TyG Index is comparable and in fact a better indicator of insulin resistance and thereby metabolic dysfunction as opposed to HOMA-IR with a p-value of <0.05 (Table 7).

Discussion

Chapter V: Discussion

Prediabetes is a state of hyperglycaemia whereby blood glucose levels are too low to be considered as diabetes but also too high to be considered as normoglycaemia. Thereby, it is also termed as "intermittent hyperglycemia". Prediabetes is associated with several micro as well as macrovascular complications, mainly cardiovascular disease, nephropathy including chronic kidney disease and neuropathy as well (Bansal N, 2015).

Nearly 26-50% of individuals with prediabetes are prone to develop overt diabetes over the course of time if left neglected/untreated[2]. Hence, lifestyle modifications and prompt medical interventions mainly with adherence to medication targeted at achieving weight loss and consequently early insulin resistance could bring promising results with almost 40-50% relative risk reduction of complications (Nathan DM et al., 2007).

So, early detection of prediabetes and insulin resistance is of paramount importance if we aim to achieve a significant reduction in complications. This detection strategy should be cheap, affordable, reliable, and accessible to the patients and can be reproduced in regular clinical settings if we want to achieve our primary objective. TyG index is a cheaper, affordable, reliable, and effective alternative to the more expensive tests like HbA1c and HOMA-IR for detecting prediabetes and insulin resistance respectively (Cline GW et al., 1999). It also has the additional benefit that we can derive both the lipid and glycaemic status of the individual with a single fasting blood sample which also improve patient compliance and thereby early detection could lead to early prevention of diabetes related complications (Simental-Mendia LE et al., 2008). To our knowledge this is the first such population-based study that has been done in the Bangladeshi Population till date involving prediabetes patients using TyG index as a risk marker.

The results of our study showed that the Area under the Curve (AUC) demonstrated a higher ROC AUC score for HbA1c (0.923) as compared to the TyG Index (0.874) for diagnosing prediabetes. These values were further validated with the Youden's index which further demonstrated the afore-mentioned variations between HbA1c and TyG index (0.73 vs 0.66), but the differences were not statistically significant with a p-value of 0.062. The cut-off point for HbA1c was >5.53 with a maximum sensitivity of

0.912 and sensitivity of 0.820 for the diagnosis of prediabetes while the cut-off point for TyG Index was >4.762 with a maximum sensitivity of 0.845 and specificity of 0.805 respectively (Figure 6). These results are similar to recent studies conducted in India which shows similar cut-off points for HbA1c and TyG index in prediabetes individuals and thereby also ascertains the validity of the results in our population (Darshan V et al., 2022), (Selvi NMK et al., 2021). Both these differences in the cut-off point sensitivities and specificities were highly statistically significant for the diagnosis of prediabetes and further demonstrates that TyG index is comparable to HbA1C for the diagnosis of prediabetes. This study is unique in the sense that is one of the first studies that has been done to demonstrate the efficacy of TyG index as compared to HbA1c in prediabetes.

A cohort study in Korea showed a positive correlation of developing diabetes with increasing TyG indices even suggesting that Tyg index can be used as a reliable risk marker to track the progression of the relative risk and incidence of DM over the course of time even after adjusting for the conventional risk factors for DM (S. H. Lee et al., 2014). Consequently, another study showed that TyG index was even better than FPG and TG levels in predicting and identifying patients suspected with a high risk of developing diabetes (M. Zhang et al., 2017).

The mechanisms suggesting the correlation between TyG and DM are complex. It has been hypothesized that it could be due to increased fatty acid content because of elevated triglyceride levels thereby resulting in a shift of free fatty acids from adipose tissue to its non-adipose tissue counterpart which consequently disrupts the glycaemic status of the individual (Parhofer KG, 2015). Also, high hepatic and skeletal muscle triglyceride levels may also affect organ specific glucose metabolism (Kelley DE et al., 2001), (Nagle CA et al., 2009). Chronic inflammation in the form of proinflammatory cytokines and oxidative stress could also result as a consequence of chronic hyperglycaemia resulting in cellular damage. This process is called glucometabolic disorder (Rodriguez F et al., 2016). Obesity, especially visceral obesity, has also been linked with hyperglycemia in the background of insulin resistance which could further lead to the development of T2DM and future cardiovascular events (Frayn KN, 2000).

Elevated triglycerides could also alter the gastric or neural pathways that are responsible for glycaemic control (Lebovitz HE et al., 2013). Several studies have found a positive correlation between dyslipidemia and glycaemic control (Parhofer KG, 2015). Recent studies have also highlighted the role of high triglycerides and its association with HbA1c and TyG index could be used as a future marker to associate dyslipidemia with micro and macrovascular complications in T2DM patients (Hussain A et al. 2017). TyG index is also reported to be a highly specific and sensitive marker of identifying metabolic syndrome, insulin resistance as well as macrovascular disease and these findings could further cement its role as a potent marker that links T2DM with CVD (Mohd Nor NS et al., 2016), (Lee EY et al., 2016).

Diabetic Dyslipidemia is characterized by elevated triglycerides, low HDL-cholesterol, and high small-dense LDL particles (Parhofer KG, 2015). These alterations in the lipid parameters are not only a consequence of glucose metabolism impairment but also the causative agent. The mechanisms of high FFAs in these patients could be attributed to the following reasons:

1. Elevated TG inducing insulin resistance and β-cell dysfunction.
2. Disruption of GLUT transporters with insulin receptor cascades.
3. Subclinical inflammation resulting from pro-inflammatory adipokine release by adipocytes (Lee Y et al., 1994), (Rachek LI, 2014).

Our study also demonstrates that the Pearson correlation coefficients between the various anthropometric measurements related to insulin resistance with TyG Index and HOMA-IR demonstrated a highly significant difference in weight (0.186 vs 01.54) in favor of TyG Index with a p-value of <0.01 and a significant difference in Body Mass Index (0.421 vs 0.372), Waist Circumference (0.286 vs 0.253) and Waist to height Ratio (0.392 vs 0.333) which further demonstrates that TyG Index is comparable and in fact a better indicator of insulin resistance and thereby metabolic dysfunction as opposed to HOMA-IR with a p-value of <0.05. These studies are consistent with previous population based studies that have been done in prediabetes patients comparing TyG index and HOMA-IR (Darshan V et al., 2022), (Selvi NMK et al., 2021).

Prediabetes is characterized by insulin resistance in the background of pancreatic β-cell dysfunction (Rachek LI, 2014). Glucose and lipid metabolism homeostasis is

maintained by adipocytes and adipose tissue which are responsible for secreting hormones and cytokines that are involved in chronic inflammation (S. E. Kahn, 2003). In the fed state, triglycerides are stored through the synthesis of adipocytes. While in the fasting state, triglycerides are released as free fatty acids and glycerol, which are then utilized by the liver and the corresponding skeletal muscle (Hajer GR et al. 2008). In the presence of Insulin Resistance, there are several cells that contribute to hyperglycaemia and elevated lipids like liver, muscle, adipose tissue and pancreatic β-cells in particular. Hypertriglyceridemia induces glucokinase activity and islet cell mediated glucose-stimulated insulin secretion. Hyperglycaemia causes oxidative stress and continuous glucose toxicity and lipotoxicity resulting in β-cell failure (Delarue J et al., 2007).

TyG index has been associated with IR and can be proposed as a reliable surrogate marker for detecting IR even in healthy individuals (Shulman GI, 2014). These findings have been validated in several recent studies. TyG index and incident diabetes have also been demonstrated in various recent studies (Shulman GI, 2014). Recent studies have also revealed the relationship between TyG index and HOMA-IR as well as the Hyperinsulinaemic-Euglycemic clamp which is considered as the Gold standard test for identifying IR (DeFronzo RA et al. 2015).

TyG index has also been proposed to be a better and more efficient marker than Visceral Adiposity Index (VAI) Lipid Accumulation products (LAP) in early stages of IR. Thereby. TyG index can also be a relative marker of both obesity and IR since they share the same etiology (Timalsina S et al., 2021).

TyG index is an independent risk marker for cardiovascular events like all-cause death, cardiac revascularization, rehospitalization due to cardiac causes & MACEs in general irrespective of diabetes and traditional risk factors for CVD. High TyG Index is also positively correlated with ischaemic stroke, obstructive sleep apnoea, hypertension, coronary artery calcification, arterial stiffness, carotid atherosclerosis, coronary artery stenosis, small vessel disease and nephric microvascular damage (Timalsina S et al., 2021), (Park K et al., 2019). Additionally, TyG index can also help to determine high-risk cardiovascular events in healthy individuals as well which could prompt preventive strategies aimed at regular exercise, diet management, weight loss and medications to prevent future cardiovascular events. TyG index can

also be used for the future development of drugs that can help to improve IR and can be used as an additional risk marker for early identification other than conventional risk factors like HbA1c or FPG in patients with insulin resistance. In a recent study, TyG index was also associated with Diabetic Nephropathy in patients with T2DM (Liu L et al., 2021). It is therefore a simple and reliable test that incorporates both glucose and lipids pathophysiology and thereby is a more sensitive indicator of insulin resistance than conventional tests.

Finally, HOMA-IR and Hyperinsulinaemic-Euglycaemic clamp test are expensive and time consuming and cannot be used in routine clinical settings especially in poor resource areas lacking standardized labs and where healthcare is dependent on the individual's economic status and accessibility. TyG index is a simple, reliable, easily reproducible, and effective test that uses only a single sample blood test and is a valid surrogate marker for IR. Several studies have validated this claim which means that is only time demanding now to use TyG index as a regular screening test for individuals suspected with prediabetes or T2DM or cardiovascular disease as well irrespective of diabetes. High TyG index also correlates with HOMA-IR with some studies proving it to a better than HOMA-IR in predicting IR. TyG index correlates with both the atherosclerotic and metabolic derangements in IR and is also comparable to the gold standard Hyperinsulinaemic-euglycaemic clamp test for IR (Guerrero RF et al., 2010) Also, previous studies have shown that TyG index is closely linked to diabetes and both macro and microvascular complications (Shulman GI, 2014).

So, the object of our study was to find an alternative solution to the available yet expensive biomarkers like HbA1c and HOMA-IR which can be easily reproducible in routine clinical settings in poor resource conditions. Consequently, our study shows that TyG index significantly correlates with both HbA1c and HOMA-IR and can be used as an alternative screening test for the diagnosis and identification of prediabetes.

Conclusion

Chapter VI: Conclusion

It is clearly evident that a comprehensive search for biomarkers to identify IR is of paramount importance in our regular clinical settings to predict prediabetes, future diabetes risk and in turn prevent complications that arise from diabetes and poor glycaemic control.

HbA1c is a reliable and effective test to identify prediabetes/diabetes as well as glycemic status, but it has its limitations of being expensive and requires a standardized lab facility which is quite difficult in a poor resource country like ours. HOMA-IR and Hyperinsulinaemic-Euglycaemic clamp are both effective but also awfully expensive and time consuming and cannot be used in routine clinical settings. So, the search for new biomarkers which are cheap, dependable, easily reproducible, and effective and is now a dire concern for us clinicians that are working in poor resource low-income countries. TyG index is one such risk marker that is a reliable surrogate marker for IR, is cheap, simple to reproduce, does not require a highly standardized lab essay, is a one sample test which is also patient compliant and is also comparable to HbA1c for monitoring glycaemic status and predicting/identifying prediabetes as well. Hence, it can be used as an alternative screening tool for the better management of high-risk individuals prone to develop prediabetes.

Strengths and Limitations

Chapter VII: Strengths and Limitations of the Study

The strengths of the present study are that the data has been collected by producing a pre structured questionnaire from the institution where the diabetic patients were physically checked-up and directly interviewed by the author himself. The author assessed the socio-economic status, demographic information, general health characteristics of 200 participants, did the documentation, data entry, data analysis and interpretation.

Strength of this study also includes the size of the sample which has been collected at narrowly defined time-period by directly face to face interview. The collected data was also associated with instantly available biochemical laboratory value provided by the participants which are related to the findings of the study.

The case control study considered matching two confounding factors like age and sex which may affect the outcome/results in observational studies.

The limitation of the Study involves the small sample size (n=200) due to resource limitations since a lot of the investigations (HbA1c and Fasting Serum Insulin) were funded by the author himself.

Secondly, this study involves only the Bangladeshi Population (specific ethnicity) and was also a single-center study (subjected to observer, selection and recall bias) so we cannot generalize the study to other populations.

Thirdly, since we could only measure a baseline FPG and TG values which we are aware are prone to change over time and with lifestyle modifications, we need to perform a time-dependent analysis.

Lastly, we did not use the gold-standard measurement of IR like the Hyperinsulinaemic-euglycaemic clamp because it is expensive and time-consuming and cannot be easily reproduced in routine clinical settings. We compensated for this limitation by using the TyG index, which is a highly sensitive, reliable and easy to detect procedure and has been widely proposed as a reliable surrogate of insulin resistance in comparison to HEGC.

Recommendations

Chapter VIII: Recommendation and future perspective

A comprehensive and multi approach study is necessary regarding large sample size, different study locations covering nationwide where all categories of citizens should be included. So, Randomized Controlled Trials from multi-center institutions need to be done to rule out observer and selection bias.

References

Chapter IX: References

Abdul-Ghani MA. Tripathy D. De Fronzo RA. Contribution of beta cell dysfunction and insulin resistance to pathogenesis of impaired glucose tolerance and impaired fasting glucose, Diabetes Care. 2006; 29:1130-1139.

Afroz, A., Alam, K., Ali, L. et al. Type 2 diabetes mellitus in Bangladesh: a prevalence based cost-of-illness study. BMC Health Serv Res 19, 601 (2019).

Akter S, Rahman MM, Abe SK, Sultana P. Prevalence of diabetes and prediabetes and their risk factors among Bangladeshi adults: a nationwide survey. Bull World Health Organ. 2014 Mar 1;92(3):204-13, 213A.

Akhtar S, Nasir JA, Sarwar A, et al. Prevalence of diabetes and pre-diabetes in Bangladesh: a systematic review and meta-analysis. BMJ Open 2020;10:e036086.

Alberti SG, Zimmet P, Shaw J, Grundy SM. IDF Consensus Worldwide Definition of the Metabolic Syndrome 2006;2-10.

American Diabetes Association (ADA).Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. Diabetes Care 2022; 45(1):17–38.

Andres R, Baltzan MA, Cader G, Zierler, KL. Effect of insulin on carbohydrate metabolism and on potassium in the forearm of man. J. Clint. Inivest 1962; 41: 108-115.

Anonymous et al. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2012;35(Suppl 1):S64-S71.

Bansal N. Prediabetes diagnosis and treatment: A review. World J Diabetes 2015;6(2):296-303.

Baron AD, Kolterman OG, Bell J, Mandarino LJ, Olefsky JM. Rates of noninsulin-mediated glucose uptake are decreased in Type II diabetic subjects. J Clin Invest 1985; 76: 1782–1788.

Bergman M, Abdul-Ghani M, Neves JS, Monteiro MP, Medina JL, Dorcely B, Buysschaert M. Pitfalls of HbA1c in the Diagnosis of Diabetes. J Clin Endocrinol Metab. 2020 Aug 1;105(8):2803–11.

Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care. 2002;25(7):1135-41.PMID: 12087010.

Canadian task force on preventive Health Care. Recommendations on screening for type 2 Diabetes in adults. CMAJ. 2012; 184(15):1687-1696.

Chiasson JL, Josse RG, and Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. Lancet 2002; 359(9323): 2072–7.

Chowdhury SR. Pre-Diabetes: Diagnostic Criteria And Therapeutic Approach. JCMCTA 2018; 29 (2):68-75.

Cline GW, Petersen KF, Krssak M, et al. Impaired glucose transport as a cause of decreased insulin-stimulated muscle glycogen synthesis in type 2 diabetes. N Engl J Med 1999; 341:240– 246.

Curb JD, Rodriguez BL, Burchfield CM, Abbott RD, Chiu D et al. Sudden death, impaired glucose tolerance, and diabetes in Japanese American men. Circulation. 1995; 15 (10):2591-5.

Darshan V, Rajput R, Mohini M, Garg R, Saini S. Comparison of triglyceride glucose index and HbA1C as a marker of prediabetes – A preliminary study. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2022; 16(9):102605

Da Silva A, Caldas AP, Hermsdorff HH, Bersch-Ferreira ÂC, Torreglosa CR, Weber B, Bressan J. Triglyceride-glucose index is associated with symptomatic coronary artery disease in patients in secondary care. Cardiovascular diabetology. 2019 Dec;18(1):1-8.

DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. American Journal of Physiology-Endocrinology And Metabolism. 1979 Sep 1;237(3):E214.

DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004; 88(4):787-835.

DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. NEJM 2011; 364(12): 1104–15.

DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. Nature Reviews. Disease Primers 2015;(1):15019.

Delarue J, Magnan C. Free fatty acids and insulin resistance. Current Opinion in Clinical Nutrition and Metabolic Care 2007;(10)2:142–148.

Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. Cardiovascular diabetology. 2014 Dec;13(1):1-0.

Ekberg K, Landau BR, Wajngot A, Chandramouli V, et al. Contributions by kidney and liver to glucose production in the postabsorptive state and after 60 h of fasting. Diabetes 1999; 48:292-298.

Frayn KN. Visceral fat and insulin resistance — causative or correlative? Br J Nutr 2000;83:S71-S77.

Genuth S, Alberti KG, Bennett P et al. Expert Committee on the Diagnosis and Classification of DM. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160-3167.

Groop LC, Bonadonna RC, DelPrato S, Ratheiser K, Zyck K, Ferrannini E, DeFronzo RA. Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. J Clin Invest. 1989;84(1):205-13.

Guerrero RF, Simental-Mendía LE, González OM, MartinezAE, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity.

Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010;95(7):3347-51.

Hajer GR, Van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. European Heart Journal 2008; 29(24):2959–2971.

Holt RIJ, Cockram CS, Flyvbjerg A, Glodstein BJ. 2017. Textbook of Diabetes 5th edition. Wiley-Blackwell Publishing. pg 217.

Hussain A, Ali I, Ijaz M, Rahim A: Correlation between hemoglobin A1c and serum lipid profile in Afghani patients with type 2 diabetes: hemoglobin A1c prognosticates dyslipidemia. Ther Adv Endocrinol Metab. 2017, 8:51–57.

International Diabetes Federation. IDF Diabetes Atlas 10th edition 2021. https://diabetesatlas.org/atlas/tenth-edition/

Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85:2402–2410.

Kawamori R, Tajima N, Iwamoto Y, et al. Voglibose for prevention of type 2 diabetes mellitus: a randomized, double-blind trial in Japanese individuals with impaired glucose tolerance. Lancet 2009; 373: 1607–14.

Kelley DE, Goodpaster BH. Skeletal muscle triglyceride an aspect of regional adiposity and insulin resistance. Diabetes Care 2001; 24(5):933e41.

Knowler WC, Fowler SE, et al. Diabetes Prevention Program Research Group, 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009; 374(9702): 1677–86.

Koliaki C, Szendroedi J, Kaul K, et al. Adaptation of hepatic mitochondrial function in humans with non-alcoholic fatty liver is lost in steatohepatitis. Cell Metab 2015; 21:739–746.

Krssak M, Brehm A, Bernroider E, Anderwald C, Nowotny P, Dalla Man C, Cobelli C, Cline GW, Shulman GI, Waldhäusl W, Roden M. Alterations in postprandial hepatic glycogen metabolism in type 2 diabetes. Diabetes. 2004;53(12):3048-56.

Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, et al. The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study). Diabetes Care 2019;42(3):416-26.

Lebovitz HE, Ludvik B, Yaniv I, et al.: Fasting plasma triglycerides predict the glycaemic response to treatment of type 2 diabetes by gastric electrical stimulation. A novel lipotoxicity paradigm. Diabetic Med. 2013, 30:687–693.

Lee SB, Ahn CW, Lee BK, Kang S, Nam JS, You JH, Kim MJ, Kim MK, Park JS. Association between triglyceride glucose index and arterial stiffness in Korean adults. Cardiovascular diabetology. 2018 Dec;17(1):1-6.

Lee EY, Yang HK, Lee J, Kang B, Yang Y, Lee SH, et al. Triglyceride glucose index, a marker of insulin resistance, is associated with coronary artery stenosis in asymptomatic subjects with type 2 diabetes. Lipids Health Dis. 2016;15(1):155.PMID: 27633375.

Lee T L; Hsuan C.F, Wu CC, Hung WC, et al. Association between Triglyceride Glucose Index and Corrected QT Prolongation in Chinese Male Steelworkers. Int. J. Environ. Res. Public Health 2021, 18, 4020.

Lee Y, Hirose H, Ohneda M, Johnson JH, McGarry JD, Unger RH. Beta cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. Proc Natl Acad Sci U S A. 1994;91(23):10878-82.

Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 2008; 371(9626): 1783–9.

Liu L, Xia R, Song X, Zhang B, et al. Association between the triglyceride–glucose index and diabetic nephropathy in patients with type 2 diabetes: A cross-sectional study. J Diabetes Investig 2021; 12 (4):557-565.

Malita FM, Karelis AD, St-Pierre DH, et al.: Surrogate indexes vs. euglycaemic-hyperinsulinemic clamp as an indicator of insulin resistance and cardiovascular

risk factors in overweight and obese postmenopausal women. Diabetes Metab 2006; 32: 251-255.

Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412–419.

Mohd Nor NS, Lee S, Bacha F, et al. Triglyceride glucose index as a surrogate measure of insulin sensitivity in obese adolescents with normoglycemia, prediabetes, and type 2 diabetes mellitus: comparison with the hyperinsulinemic-euglycemic clamp. Pediatr Diabetes 2016; 17: 458–465.

Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. American Journal of Physiology-Endocrinology and Metabolism. 2008 Jan;294(1):E15-26.

M. Zhang, B. Wang, Y. Liu et al., "Cumulative increased risk of incident type 2 diabetes mellitus with increasing triglyceride glucose index in normal-weight people: the Rural Chinese Cohort Study. Cardiovascular diabetology 2017; 16(1):30.

Nagle CA, Klett EL, Coleman RA. Hepatic triacylglycerol accumulation and insulin resistance. J Lipid Res 2009; 50(Supplement):S74e9.

Nathan MD. Diabetes Prevention Program Research Group: The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. Diabetes Med. 2007; 24(2):137-144.

Nathan DM, Davidson MB, DeFronzo RA. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diab Care.2007;30(3):753-9.

Naqvi S, Naveed S, Ali Z, et al. (June 13, 2017) Correlation between Glycated Hemoglobin and Triglyceride Level in Type 2 Diabetes Mellitus. Cureus 9(6): e1347.

Parhofer KG. Interaction between glucose and lipid metabolism: more than diabetic dyslipidemia. Diabetes Metab J 2015; 39(5):353e62.

Park K, Ahn CW, Lee SB, Kang S, Nam JS, Lee BK, Kim JH, Park JS. Elevated TyG index predicts progression of coronary artery calcification. Diabetes Care 2019 Aug 1;42(8):1569-73.

Rachek LI. Free fatty acids and skeletal muscle insulin resistance. Prog Mol Biol Transl Sci. 2014;121:267-92.

Radziuk J. Insulin sensitivity and its measurement: structural commonalities among the methods. J Clin Endocrinol Metab 2000; 85:4426–4433.

Ramachandran A, Snehalatha C, Mary S, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP 1). Diabetologia 2006; 49(2):289-97.

Rodriguez F, Mahaffey KW. Management of patients with NSTEACS: a comparison of the recent AHA/ACC and ESC guidelines. J Am Coll Cardiol 2016;68(3):313e21.

Richard EP, Glenn M. Pre-diabetes: Clinical relevance and therapeutic approach. British Journal of Diabetes and Vascular Disease. 2007; 7:120.

Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115(4):450-8.

S. E. Kahn. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003; 46(1):3–19.

Selvi NMK, Nandhini S, Sakthivadivel V, Lokesh S, Srinivasan AR, Sumathi S. Association of Triglyceride-Glucose Index (TyG index) with HbA1c and Insulin Resistance in Type 2 Diabetes Mellitus. Maedica (Bucur). 2021;16(3):375-381.

S. H. Lee, H. S. Kwon, Y. M. Park et al., “Predicting the development of diabetes using the product of triglycerides and glucose: the Chungju Metabolic Disease Cohort (CMC) study,” PLoS One 2014; 9(2):e90430.

Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006 Jul;116(7):1793-801.

Shulman GI, Rothman DL, Jue T, et al. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. N Engl J Med 1990; 322:223–228.

Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med 2014; 371:2237–2238.

Simental-Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord 2008; 6: 299–304.

Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. Diabetes. 1995 Apr;44(4):369-74.

Su WY, Chen SC, Huang YT, Huang JC, Wu PY, Hsu WH, Lee MY. Comparison of the effects of fasting glucose, hemoglobin A1c, and triglyceride–glucose index on cardiovascular events in type 2 diabetes mellitus. Nutrients. 2019 Nov 19;11(11):2838.

Tabak AG, Herder C, Rathmann W et al. Prediabetes: A high -risk state for diabetes development. The Lancet. 2012; 379(9833):2279-2290.

Timalsina S, Mahato S, Nepal S. Utility of Triglyceride- Glucose index in predicting glycemic control in type 2 diabetes mellitus. BJHS 2021;6(2)15. 1444-1448.

Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. NEJM Med 2001; 344: 1343–50.

Vermeer SE, Sandee W, Algra A, Koudstaal PJ, Dippel DW. Dutch TIA Trial Study Group. Impaired glucose tolerance increases stroke risk in nondiabetic patients with transient ischemic attack or minor ischemic stroke. Stroke. 2006; 37(6):1413-1417.

Wallace TM, Matthews DR. The assessment of insulin resistance in man. Diabet Med 2002; 19:527–534.

Weyer C, Bogardis C, Pratley RE. Metabolic characteristic of individuals with impaired fasting glucose and impaired glucose tolerance. Diabetes 1999; 48(11):2197-2203.

World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva: World Health Organization 2006.

Zhang Y, Ding X, Hua B, Liu Q, et al. High triglyceride-glucose index is associated with adverse cardiovascular outcomes in patients with acute myocardial infarction. Nutrition, Metabolism & Cardiovascular Diseases (2020) 30,2351e2362.

Zhang S, Du T, Zhang J, Lu H, Lin X, Xie J, et al. The triglyceride and glucose index (TyG) is an effective biomarker to identify nonalcoholic fatty liver disease. Lipids Health Dis. 2017;16(1):15.

Zhang X, Gregg EW, Williamson DF et al. A1C level and future risk of Diabetes: A systematic review. Diabetes Care. 2010;33:1665-1673.

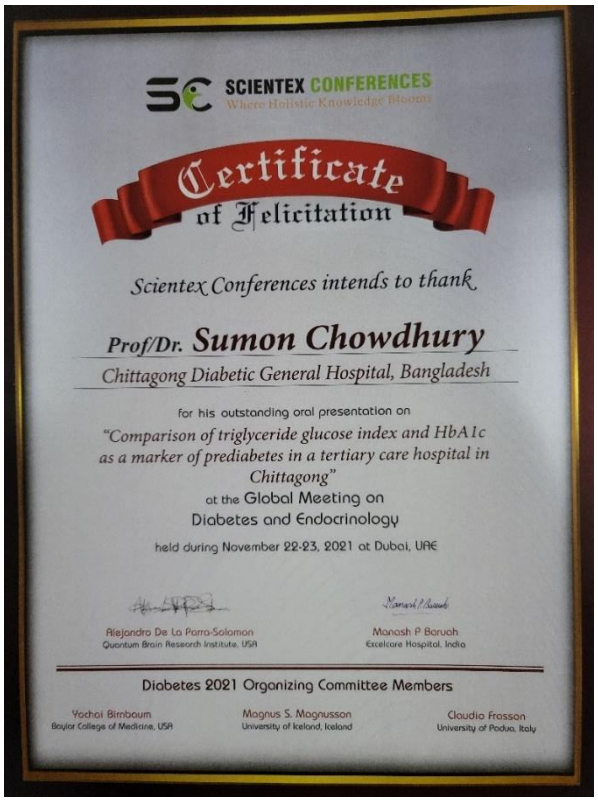
Zhang F, Tang X, Cao H, Li Q, Liu Y et al. Impaired secretion of total Glucagon like peptide-1 in people with impaired fasting glucose combined impaired glucose tolerance. Int J Med Sci. 2012; 9(7): 574-581.

Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. KORA Study Group: Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: The MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care. 2008; 31(3):464-469.

Appendices

Appendices

Annexes: Oral Presentation of " Comparison of Triglyceride-Glucose Index with HbA1c and HOMA-IR as a risk marker for prediabetes and insulin resistance in a tertiary care hospital in Chittagong" at the Global and Endocrinology Congress 2021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for his outstanding oral presentation on

"Comparison of triglyceride glucose index and HbA1c as a marker of prediabetes in a tertiary care hospital in Chittagong"

at the Global Meeting on Diabetes and Endocrinology

held during November 22-23, 2021 at Dubai, UAE

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Title : Comparison Of Triglyceride Glucose Index And HbA1c As A Marker Of Prediabetes In A Tertiary Care Hospital In Chittagong

Questionnaire

TRIGLYCERIDE GLUCOSE INDEX SURVEY

Questionnaire for MPH Thesis

Supervisor: Prof. Dr. Amam Zonaed Siddiqui

One Health Institute
Chattogram Veterinary and Animal Sciences University
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TRIGLYCERIDE GLUCOSE INDEX SURVEY

Questionnaire

1.1 Date 1.2. ID

1.3 National ID

2. Personal History

2.1 Name

2.2 Age in years

2.3 Sex (1. Mail 2. Female) 2.4 Marital Status (1. Married 2. Single 3. Others)

2.5 Occupation

1.Service holder 2. Business 3. Skilled labor 4. Manual Labor 5. Homemaker

6. Farmar 7. Unemployed 8. Student 9. Other

2.7 Religion - 1. Muslim 2. Hindu 3. Christian 4. Buddhist 5. Others

2.8. Address

2.8.1 Village/ Ward 2.8.2 Upazila

2.8.3 District 2.8.4 Division

2.9 Phone Number

2.9.1Mobile

3.0 Educational Status (yes of education) 1. Illiterate 2. Primary 3. Secondary

4. College 5. University

TRIGLYCERIDE GLUCOSE INDEX SURVEY

4. Physical Activity level (minutes per day):

4.1 physical activity leisure time: no/yes (walking < 30 min/day/ 30-60 min/ > 60 min)

5. Socio- economic History

5.1 Earning capacity (1. Earner 2. Dependent)

5.2 Total monthly expenditure of family (< 10000 BDT/10000-20000 BDT/ > 20000 BDT)

6. Personal History

6.1 **Family history of DM** (Yes = 1, No = 2, Unknown = 3)

	1	2	3
Father			
Mother			
Brother/sister			
Sons/ daughters			

6.2 Personal Habit (s) (Ex = more than 6 months)

Name	(1. Y 2 N 3. Ex	No/ Amount	Name	(1. Y 2 N 3. Ex	No/ Amount
A. Cigarettes			D. Alcohol		
B .Chews Tobacco			E. Other		

7. Past Medical History

Sl	Name of Diseases	(Yes =1, No = 2, Unknown = 3) & date of diagnosis	Are you currently taking any medication (1 Yes 2. No)	Medicine Name
1.	High blood pressure			
2.	Stroke			
3.	Heart Attack/ IHD			
4.	Foot ulceration			
5.	Claudication			
6.	Vision problem			
7.	TB			
8.	Kidney disease			
9.	Other specify			

TRIGLYCERIDE GLUCOSE INDEX SURVEY

8. Symptoms of DM at diagnosis at registration (✓)

☐ Yes No ☐

If yes, increased urination ☐ Increased thirst ☐ Increased hunger ☐

Weight loos ☐ General weakness ☐

9. Physical Examination

9.1 Blood pressure SPB ☐ DBP ☐

9.2 Weight in kg ☐ 9.3 Height in cm ☐

9.4 Waist in cm ☐ 9.5 Hip in cm ☐

10. Investigations

No	Name of the test	Result
1	FPG level (mmol/l)	
2.	2hAG. 2hAB (mmol/l)	
3.	HbA1c %	
4.	Fasting Serum Insulin	
5.	Fasting Serum Triglyceride	

11. **Dietary history**: (how many times you eat these foods)

No	Type	Day	Week	Month	Times
1.	Green Vegetable				
2.	Fruits				

12. Management

	Treatment	Drug name	Dose
1.	Only Lifestyle		
2.	Oral hypoglycemic agent: Metformin/ Sulphonylurea/ Glucosidase inhibitor/ DPP-4 inhibitors/ SGLT-2 inhibitors		
3.	Insulin: FA/SA/RA/ Premix/split mixed/ Basal bolus/ Basal only		
4.	Anti-hypertensive drug: BB/CCB/ACE-I/ARB/ Alpha-blocker/ Diuretics		
5.	Anti-lipids: Statin/ Fibrate/ Ezetimibe		

Name & Signature .....

TRIGLYCERIDE GLUCOSE INDEX SURVEY

সম্মতি পত্র

র‍্যান্ডম ব্লাড সুগার পরীক্ষার দ্বারা ডায়াবেটিস নির্ণয় ও চিকিৎসা প্রদান বিষয়ক গবেষণা প্রকল্পে অংশগ্রহণের জন্য আপনাকে আমন্ত্রণ জানানো যাচ্ছে। গবেষণাটি সম্পর্কে তথ্য প্রদানের জন্য এই পত্রটি তৈরি করা হয়েছে। পর্যবেক্ষক নিজে অথবা তার প্রতিনিধি আপনার কাছে গবেষণাটি সম্পর্কে বিস্তারিত জানাবেন এবং আপনার যদি কোন প্রশ্ন থাকে তার উত্তর দেবেন।

প্রকল্প শিরোনাম ঃ TRIGLYCERIDE GLUCOSE INDEX SURVEY

পর্যবেক্ষক ----------

ঠিকানা ----------

ফোন নম্বর ----------সহকারী পর্যবেক্ষক ----------

আমি ---------- র‍্যান্ডম ব্লাড সুগার পরীক্ষার দ্বারা প্রিডায়াবেটিস নির্ণয় ও চিকিৎসা প্রদান বিষয়ক গবেষণা প্রকল্পে একজন সেচ্ছাসেবী হিসাবে অংশগ্রহণ করতে সম্মত।

আমি উপরোল্লিখিত গবেষণার উদ্দেশ্য সম্পর্কে জ্ঞাত এবং আমাকে জানানো হয়েছে যে, উন্নত দেশগুলোর তুলনায় বাংলাদেশের মতো উন্নয়নশীল দেশগুলোতে ডায়াবেটিক রোগটি দ্রুতহারে বৃদ্ধি পাচ্ছে আর এর সাথে সাথে বেড়ে চলছে ডায়াবেটিসজনিত বিভিন্ন জটিলতা যেমন পক্ষাঘাত, হৃদরোগ, পায়ে পচনশীল ক্ষত, অন্ধত্ব, কিডনীর কার্যক্ষমতা লোপ পাওয়া।

বর্তমানে বাংলাদেশে শিরার রক্তের মাধ্যমে খালি পেটে, ৭৫ গ্রাম গ্লুকোজ গ্রহণের ২ ঘন্টা এবং বিশেষায়িত হাসপাতাল/ক্লিনিক এ এইচ বিএ১সি পরীক্ষার মাধ্যমে প্রিডায়াবেটিস নির্ণয় ও চিকিৎসা প্রদান করা হয়। এর পাশাপাশি, এই অধ্যয়নের লক্ষ্য হচ্ছে ট্রাইগ্লিসারাইড গ্লুকোজ (এঞুএ) সূচক এবং ঐনঅ১ঈ কে প্রিডায়াবেটিসের একটি ডায়াগনস্টিক চিহ্নিতকারী হিসাবে তুলনা করা যাতে প্রাথমিকভাবে নির্ণয়ের ফলে ডায়াবেটিস মেলিটাসের আরও অগ্রগতি রোধ করার জন্য প্রয়োজনীয় ব্যবস্থা গ্রহণ করা যায়।

আমাকে জানানো হয়েছে, গবেষণায় নিয়ম অনুযায়ী শারীরিক পরীক্ষা ও ২ চা চমচ পরিমাণ শিরার রক্ত নেয়া হবে।

আমি আরো জানি যে, আমার কাছে থেকে যেসব তথ্য সংগ্রহ করা হবে সেগুলো গোপন রাখা হবে।

আমার অংশগ্রহণ সম্পূর্ণ স্বেচ্ছাসেবামূলক এবং এই প্রশ্নমালার যেকোন প্রশ্নের উত্তর না দিতে অপরাগতা প্রকাশে আমি স্বাধীন। আমি ও গবেষণায় অংশগ্রহণে রাজি হয়েও যে কোন সময়ে অংশগ্রহণ থেকে সরে আসতে পারি। এই সম্মতিপত্রে আমার/আমার অভিভাবকের স্বাক্ষর নির্দেশ করে যে আমি আপনাদের প্রত্যাশা বুঝতে পেরছি এবং এই গবেষণায় অংশ নিতে রাজি আছি। আমি জানি যে, আমাকে চাওয়া মাত্র এই সম্মতিপত্রের একটি কপি সরবরাহ করা হবে।

অংশগ্রহণকারী অথবা তার প্রতিনিধির স্বাক্ষর ও তারিখ

10.3 Brief Biography

Dr. Sumon Rahman Chowdhury completed his MD and graduated “cum laude” from University of Debrecen, Medical and Health Science Center, Hungary in 2005. He further completed his Postgraduate Diploma in Diabetes from Cardiff University, UK in 2014 and graduated with “Distinction” grade. He later completed his MMed in Endocrinology under CSC Government Scholarship from Shandong University Cheeloo College of Medicine, Shandong, China and graduated as an “Excellent Graduate” in 2016. He is currently working as a Registrar in the Dept. of Endocrinology, Diabetes and Metabolism at Chittagong Diabetic General Hospital, Chittagong, Bangladesh with over 14 years of experience in treating patients with Diabetes and Endocrine Disorders and pursuing his MPH from Chittagong Veterinary and Animal Sciences University. Dr. Sumon Rahman Chowdhury has authored 39 articles in Local and International journals with topics pertaining to Diabetes and Endocrine disorders and has deliberated several seminars and case presentations in various conferences both at home and abroad. His areas of expertise involve Diabetes and Chronic Complications and Biomarkers of Diabetic Retinopathy. He has also authored a book on “Biomarkers of Diabetic Retinopathy” published by Lambert Academic Publishing, Germany.