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Assessment of symptoms and complications in treatment of naive newly diagnosed type 2 diabetes mellitus and their correlation with glycemic parameters

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***Abstract*---**Introduction: Diabetes mellitus (DM) is a metabolic disorder that occurs in the body because of decreased insulin activity and/or insulin secretion. Pathological changes such as nephropathy, retinopathy, and cardiovascular complications inevitably occur in the body with the progression of the disease. DM is mainly categorized into 2 sub-types, type I DM and type II DM. While type I DM is generally treated through insulin replacement therapy, type II DM is treated with oral hypoglycaemics.

***Keywords*---**Microvascular complications, Glycemic control, Type 2 diabetes mellitus, Prevalence.

Introduction

The natural history of type 2 diabetes is hallmarked by progressive loss of beta-cell function coupled with increased insulin resistance. This is thought to be due to the combined toxic effects of hyperglycemia and increased free fatty acids (glucolipotoxicity). [1] The shorter and less severe the glucolipotoxicity insulin, the more beta-cell preservation and/or recovery can be expected. A higher beta-cell function has been associated with improved glycemic control, less treatment burden, and fewer microvascular complications. [2]

The Origin Trial explored whether early use of insulin glargine, compared to standard of care treatment, in patients with impaired fasting glucose, impaired glucose tolerance, or newly-diagnosed type 2 diabetes can prevent disease progression. [3] In the 1200 patients without diabetes, those who were assigned to insulin glargine were 25% less likely to develop diabetes during the 6.2 years of follow-up, an effect presumed to be due to stabilization/improvement in beta-cell function. While this approach did not show an overall decrease in cardiovascular events during the study follow-up, a proactive treatment approach, very early in the course of the disease, could have longer term impact on the disease course, and thus be superior to the current reactive approach where treatment is only initiated or escalated as the disease worsens. [4]

Short-term (2– 3 weeks) intensive insulin treatment has been shown to result in disease remission in some patients, especially those with newly-diagnosed diabetes. Unfortunately this approach alone, without subsequent treatment, is not durable as >40% of patients required additional treatment by one year. [5] compared a short course of oral therapy to insulin therapy in patients with newly diagnosed type 2 diabetes. After normoglycemia was attained, treatment was discontinued and patients followed for one year. Fewer patients reached control (83.5% vs 95– 97%) or attained remission at one year (25% vs 40–50%) in the oral group, [6] suggesting that initial insulin treatment may have a stronger beta-cell preservation effect, yet still not sufficient to change the course of the disease long-term in the absence of subsequent therapy. Therefore, short-term intensive treatment, whether with insulin or oral hypoglycemic agents, in the absence of subsequent maintenance treatment is not sufficient to preserve beta-cell function long term. Chen et al performed a study where both groups received initial insulin therapy followed by randomized to oral therapy or insulin. The insulin group preserved more beta-cell function at 6-months but it is unclear if this was due to the treatment received or the glycemic targets achieved (the oral group had significantly higher HbA1c throughout the study). [7]

Long-term studies in patients with newly-diagnosed diabetes evaluated diet therapy, monotherapy with metformin, sulfonylureas, or glitazones, but none of these monotherapy interventions were successful in stabilizing the disease process [8] beyond the initial 6– 18 months. There are no long-term studies to investigate

whether insulin is superior to an intensive oral therapy in preserving beta-cell function, especially when similar glycemic control is maintained between groups.

We evaluated whether short term (3-month) pharmacotherapy followed by either continued insulin regimen versus a multi-drug oral regimen can achieve and maintain long-term (6-year) glycemic control and preserve beta-cell function. Safety and quality of life parameters were also compared.

Material and Methods

This was a prospective, cross-sectional, single-arm observational study. We determined the clinical and glycemic parameters in treatment naïve newly diagnosed type 2 diabetes with HbA1c >9% at diagnosis. Institutional clearance from the ethics board was obtained as per the standard protocol.

Inclusion criteria

The study population was the consecutive outpatients presenting to a general tertiary care hospital over a period of 8 months. The study comprised a total of 60 cases of treatment naïve patients with new-onset type 2 diabetes between the age group of 20 and 70 years of either gender with HbA1c >9% at the time of diagnosis.

Exclusion criteria

- Type 1 diabetes/pancreatic diabetes/fibro calculous pancreatic diabetes
- Age younger than 20 years or older than 70 years
- Patients with emergencies - acute myocardial infarction/unstable angina/non - ST- elevation myocardial infarction/stroke/pancreatitis/diabetic ketoacidosis/hyperosmolar nonketotic coma/surgical emergencies.
- Patients on chronic steroid medications for malignancy/asthma/rheumatoid arthritis
- HbA1c <9% at diagnosis.

Clinical data

All the history and basic clinical examination were done by the same observer. A preset, pro forma was used to maintain the uniformity in the history collection and physical examination. The data for this cross-sectional study contained patients' age, gender, family history of diabetes, history of comorbid illness, and symptoms at the time of presentation. For each patient, we screened for the presence or absence of diabetes complications. Height was measured from a wall-mounted and fixed stadiometer, nearest to 0.1 cm was taken as the height of the subject with the subjects' head in the Frankfurt's plane. Weight was measured with an electronic weighing scale by Omron. Reading to the nearest of

0.1 kg was recorded as the weight of the subject. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared.

Blood pressure was recorded to the nearest 2 mmHg in the sitting position in the right arm with a mercury sphygmomanometer. Two readings were taken 5 min apart, and the mean of the two was calculated. Variations in blood pressure measurements were minimized by (1) ensuring 10 min rest before the recording, (2) using appropriate adult cuffs for lean and overweight individuals, and (3) having the same observer recording blood pressure. Fundoscopy was performed by an ophthalmologist after dilatation of pupils with tropicamide, the ophthalmologist was blinded to the study.

All patients were examined, with special attention for the presence or absence of markers of insulin resistance skin tags and acanthosis nigricans, goiter graded according to WHO criteria along with examination of peripheral pulses.

Biochemical

Glucometer RBS was measured irrespective of the meal status using the commercially available Alere Glucometer. FBS and PPBS (glucose oxidase-peroxidase method) were measured on a Autoanalyzer. HbA1c was estimated by high-pressure liquid chromatography using the Variant machine (Bio Rad D-10). Creatinine was measured in the commercially available Autoanalyzer Turbo-Chem 100.

Statistical analysis

Statistical analysis was done by estimating the symptoms in treatment naïve newly diagnosed type 2 diabetes and correlating with glucose parameters. All the statistical analysis were done using the software STATA 23.0. Descriptive statistics such as percentages and frequencies were used in the data summaries. The extent to which this correlation coefficient can show a significance was given in terms of *P* value. $P < 0.05$ was taken as statistically significant and the data were represented in the form of tables and graphs.

Result

Over the 8-month study period, a total of 60 treatment naïve newly diagnosed T2DM patients were included.

Table 1
Distribution of Gender

Gender	n (%)
Male	**39 (65.0%)**
Female	**21 (35.0%)**
Total	**60 (100%)**

In table 1, of the 60 samples, 39 were males and 21 females, which correspond to 65.0% of male and the rest female.

Table 2
Distribution of the number of subjects according to age group

Age group	n (%)
30-40 years	**10 (16.6%)**
41-50 years	**21 (35.0%)**
51-60 years	**29 (48.3%)**
Total	**60 (100%)**

In this study, the maximum number of patients were in the age group of 51-60 years which were 48.3% (n =29) of total followed by age group 41– 50 years having 35.0% (n = 21) followed by age group 30-40 years with 16.6% (n=10) in table 2.

Table 3
Summary statistics of Complications Observed in Subjects

Parameter	N (Percentage)
Comorbidities n (%)	
New Diagnosis Hypertension	13 (21.6)
New Diagnosis Hypertension + Hypothyroid	2 (3.3)
CAD with Hypertension	2 (3.3)
CAD + AKI with Hypertension	1 (1.6)
Hypertension with Hypothyroid	2 (3.3)
Hypothyroid with PCOD	1 (1.6)
Pulmonary Koch	1 (1.6)
Kidney Disease *n* (%)	
Chronic Kidney Disease	4 (6.6)
Diabetic Retinopathy *n* (%)	
Non-Proliferative Diabetic Retinopathy	3 (5)

Demographics and clinical characteristics of subjects were categorized based on the presence or absence of complications at the time of diagnosis. Out of total of 60 subjects, 29 subjects (48.3%) had complication and 31 subjects (51.6%) did not have any complications. The most frequently observed complications in our study were hypertension (21.6%) followed by chronic kidney disease (CKD) (6.6%) and non-proliferative diabetic retinopathy (5%) respectively in table 3.

Table 4
Summary statistics of glycemic parameters in subjects with complications

Parameters	**Mean±SD**
Random Blood Sugar Level by Glucometer (GRBS-mg/dl)	300.23±90.16
Fasting Blood Sugar Level (FBS - mg/dl)	148.67±21.21
Post Prandial Blood Sugar Level (PPBS - mg/dl)	301.83±34.23
HbA1C (%)	8.52±1.23
Creatinine (mg/dL)	1.07±0.34
eGFR	50.35±7.29

Table 4 outlines the summary of the statistics of glycemic parameters in subjects with complications. The average of glycemic parameters including GRBS, FBS, and PPBS was reported to be 300.2, 148.6 mg/dl, and 301.8 mg/dl, respectively. The mean of HbA1c at diagnosis was 8.52% and the mean creatinine was found to be 1.07 mg/dl.

Table 5
Summary statistics of symptoms and conditions in subjects with complications

Parameter	**n %**
Polyuria/Polyphagia/Polydypsia	10 (16.6)
Nocturia	11 (18.3)
Weight Loss	13 (21.66)
Balanitis/Vulvovaginitis	7(11.6%)
Retinopathy	1(1.66%)
Giddiness	4 (6.6%)
Absent	10(16.6%)
Paresthesia/Tingling/Numbness	7 (11.6%)
Acanthosis Nigricans	
Present	10(16.6%)
Grade 1	4
Grade 2	3
Grade 3	3
Skin Tags *n* (%)	
Present	4 (6.6%)

As shown in Table 4, the most observed symptoms in subjects with complications were weight loss (13, 21.6%) followed by nocturia (11, 18.3%), polyuria (10, 16.6%), balanitis (7, 11.6%), paranesthesia (7, 11.6%), giddiness (4, 6.6%), and retinopathy (4, 6.6%). Out of total 10 patients with complications, varying grades of acanthosis nigricans was observed in 10 patients (16.6%) and skin tags were observed in 4 patients (6.6%).

Discussion

Observational studies have reported a prevalence of hyperglycemia and diabetes ranging from 30% to 40% in hospitalized patients, [9] and in 65-75% of those with diabetes who have a critical illnesses or cardiac surgery. [10] A 2017 report using point-of-care bedside glucose tests data in almost 3.5 million people (653,359 ICU and 2,831,436 non-ICU) from 575 hospitals in the United States reported a prevalence of hyperglycemia, (defined as a glucose level >180 mg/dl [10.0 mmol/l]) of 32.2% in ICU patients and in 32.0% of non-ICU patients. [11]

These numbers included those with newly identified or stress hyperglycemia as well as those with a prior diagnosis of diabetes. The American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) consensus on inpatient hyperglycemia defined stress hyperglycemia or hospital-related hyperglycemia as any blood glucose concentration >140 mg/dl (>7.8 mmol/l) in patients without a prior history of diabetes. [12] Although stress

hyperglycemia typically resolves as the acute illness or surgical stress abates, a significant proportion (up to 60% in some reports) had confirmed diabetes at 6-12 months after discharge. [13] A guide from the UK on the management of □diabetes at the front door' , also recommends that any individual with diabetes who presents acutely unwell should have a capillary glucose measurement and blood/urine ketone measurement taken, but that if it is high on admission (i.e., >140mg/dl [7.8 mmol/l]) and subsequently goes down to normal, then a diagnosis of stress hyperglycemia should be made and documented to the primary care team. [14]

Measurement of HbA_{1c} is indicated in people with hyperglycemia without a history of diabetes to differentiate between stress induced hyperglycemia and previously undiagnosed diabetes. [15] The Endocrine Society and the UK Joint British Diabetes Societies for Inpatient Care recommendations indicate that people hospitalized with both an elevated blood glucose >140 mg/dl (7.8 mmol/l) and an HbA_{1c} of 6.5% (48 mmol/mol) or higher can be identified as having diabetes. [16]

In subjects without diabetes during the fasted state, plasma glucose is maintained between 70 – 100 mg/dl (3.9 – 5.6 mmol/l) by a finely regulated balance between hepatic glucose production and glucose utilization in peripheral tissues. Maintenance of normal glucose concentration is essential for cardiovascular functioning as well as central nervous system function because the brain can neither synthesize nor store glucose [17].

Systemic glucose balance is maintained by a dynamic, minute-to-minute regulation of endogenous glucose production and of glucose utilization by peripheral tissues. Glucose production is accomplished by gluconeogenesis or glycogenolysis primarily in the liver and to a lesser degree by the kidneys [17]. Gluconeogenesis results from conversion of non-carbohydrate precursors such as lactate, alanine, and glycerol to glucose in the liver. Excess glucose is polymerized to glycogen, which is mainly stored in the liver and muscle. Hyperglycemia develops because of three processes: 1) increased gluconeogenesis, 2) accelerated glycogenolysis, and 3) impaired glucose utilization by peripheral tissues. [18]

From the quantitative standpoint, inappropriately increased hepatic glucose production represents the major pathogenic disturbance. Increased hepatic glucose production results from the high availability of gluconeogenic precursors including the amino acids alanine and glutamine, as a result of accelerated proteolysis and decreased protein synthesis; lactate as a result of increased muscle glycogenolysis; and glycerol as a result of increased lipolysis; and from the increased activity of gluconeogenic enzymes (phosphoenol pyruvate carboxykinase, fructose-1,6-bisphosphatase, and pyruvate carboxylase). [19]

Glucose metabolism is maintained by an interaction of glucoregulatory hormones – insulin and counter-regulatory hormones (glucagon, cortisol, catecholamines and growth hormone). Insulin controls hepatic glucose production by suppressing hepatic gluconeogenesis and glycogenolysis. [20] Depending on the concentration in the circulation, insulin promotes protein anabolism in insulin-sensitive tissues such as muscle, glucose uptake and glycogen synthesis, and inhibits

glycogenolysis and protein breakdown. In addition, insulin is a powerful inhibitor of lipolysis, free fatty acid oxidation, and ketogenesis. [21]

Conclusion

Out of eight commonly observed symptoms at diagnosis only three symptoms nocturia, weight loss, and polyuria were associated with higher glycemic levels at presentation. We concluded that about 21.8% of patients presented with complications at the time of diagnosis. Hypertension was the most common associated comorbidity whereas complications such as CKD and no proliferative diabetic retinopathy were the commonly observed microvascular complications in our study. Although both patient with and without complications present with similar set of symptoms at diagnosis, clinical screening for target organ damage – retinopathy, neuropathy, and nephropathy is essential in newly diagnosed people with diabetes. Hypertension with higher creatinine at diagnosis is one of the ominous signs of harboring one or more underlying complication.

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