Global Journal of Medical and Pharmaceutical Sciences
Website: https://grpublishing.org/
ISSN (*online*): 2957-3629
ISSN (*print*): 2957-3610

OPEN ACCESS
Volume-1 | Issue-3 | Sep-Oct-2022 |

Original Research Article

Impact of Glycemic Control on Microvascular Complications in Type 2 Diabetes Mellitus Prospective Cohort Study

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Abstract: ***Background*:** Microvascular complications are a major concern for patients with Type 2 Diabetes Mellitus (T2DM). The impact of glycemic control on these complications remains a pivotal area of research.***Methods***: This prospective cohort study enrolled 1200 patients with T2DM,assessing the effects of glycemic control on the incidence and progression of nephropathy, retinopathy, and neuropathy over five years. Glycemic control was monitored by quarterly measurements of HbA1c.Results: Improved glycemic control was associated with a decrease in the development of microvascular complications.Specifically, the incidence of nephropathy and neuropathy decreased significantly with better control of HbA1c (OR = 0.85, p=0.01 and OR = 0.75, p<0.001, respectively). The study also noted a 20% decrease in the risk of retinopathy (OR = 0.80, p=0.002). These associations held true across various age groups, with more pronounced benefits in patients over 50 years. ***Conclusion***: Effective management of blood glucose levels is crucial for preventing microvascular complications in T2DM. The findings advocate for individualized treatment plans to achieve optimal glycemic control, thereby enhancing outcomes and reducing complications.

Keywords: Type 2 Diabetes Mellitus, glycemic control, microvascular complications, HbA1c, prospective cohort study.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by high blood glucose levels due to insulin resistance and inadequate insulin secretion [1]. It affects millions of people worldwide, significantly impacting their quality of life due to both macrovascular and microvascular complications [2]. Among the latter, nephropathy, retinopathy, and neuropathy represent the main threats to the well-being of patients, increasing morbidity and mortality [3]. Glycemic control, defined as the management of blood glucose levels to near-normal ranges, is pivotal in the management of diabetes and prevention of its complications [4]. This introduction provides a comprehensive overview of the literature exploring the impact of glycemic control on microvascular complications in T2DM, providing a foundation for the presented prospective cohort study.

Epidemiologically, diabetes continues to be a global concern. The International Diabetes Federation estimates that approximately 537 million adults were living with diabetes in 2021, a number projected to rise to 783 million by 2045 [5]. The economic impact is equally staggering, with healthcare expenditures exceeding USD 966 billion in 2021 [6]. These figures underscore the necessity for effective management strategies, including optimal glycemic control.

The linkage between hyperglycemia and microvascular complications in diabetes is well-documented. The landmark Diabetes Control and Complications Trial (DCCT) for type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes unequivocally demonstrated that improved glycemic control significantly reduces the risk of microvascular complications [7, 8]. These foundational studies have influenced clinical practice guidelines globally, advocating for stringent glucose control as a means to mitigate the risk of diabetic complications [9].

In T2DM, microvascular complications are particularly insidious, often developing silently and becoming well-established by the time of diagnosis [10]. Diabetic nephropathy, the leading cause of end-stage renal disease, affects approximately 40% of individuals with diabetes and significantly contributes to morbidity and mortality [11]. Diabetic retinopathy, on the other hand, is the most common cause of new cases of blindness among adults aged 20–74 years [12]. Diabetic neuropathy also poses significant challenges, affecting up to 50% of individuals with diabetes and leading to

foot ulcers that may require lower limb amputation [13].

Achieving and maintaining good glycemic control is central to the prevention of these debilitating complications. Several key mechanisms have been proposed to explain the impact of hyperglycemia on microvascular integrity, including increased polyol pathway flux, intracellular formation of advanced glycation end-products (AGEs), increased expression of the receptor for AGEs, activation of protein kinase C isoforms, and overactivity of the hexosamine pathway [14]. These biochemical and molecular changes contribute to structural and functional changes in the microvasculature, impairing blood flow and nutrient exchange.

Recent studies have further refined our understanding of the glycemic thresholds necessary for the prevention of complications. The ACCORD, ADVANCE, and VADT studies have highlighted the complexity of glycemic targets, suggesting that overly aggressive glucose lowering may not provide additional benefits and could be associated with increased risk of hypoglycaemia [15-17]. These findings emphasize the need for individualized glycemic targets, taking into account the patient's overall health status, risk of hypoglycemia, and life expectancy [18].

Furthermore, the duration of diabetes plays a crucial role in the development of microvascular complications. The concept of "metabolic memory" or "legacy effect", first noted in the DCCT/EDIC studies, suggests that early glycemic control can have long-lasting benefits in reducing complications [19]. This has profound implications for the timing of intervention and highlights the importance of early diagnosis and management.

In addition to traditional glycemic metrics such as fasting blood glucose and HbA1c, newer indices such as glycemic variability and postprandial glucose excursions are gaining attention [20]. These measures may provide additional insights into the risk of complications beyond what can be inferred from HbA1c alone, particularly in predicting retinopathy and neuropathy [21].

The current study aims to further elucidate these relationships through a prospective cohort analysis of individuals with T2DM, focusing on how variations in glycemic control influence the progression of microvascular complications over time. By integrating robust longitudinal data, the study seeks to provide actionable insights that can guide clinical practice and patient management in diabetes care.

AIMS AND OBJECTIVES

The primary aim of this prospective cohort study was to assess the impact of glycemic control on the development and progression of microvascular complications in patients with Type 2 Diabetes Mellitus (T2DM) over a five-year period. The objectives were twofold: firstly, to quantify the relationship between baseline HbA1c levels and the onset of nephropathy, retinopathy, and neuropathy in this patient population; secondly, to evaluate the influence of changes in glycemic control, as reflected by HbA1c fluctuations, on the progression of these microvascular complications.

MATERIALS AND METHODS

The study was conducted at multiple centers across North America and Europe, ensuring a diverse patient demographic. Subjects eligible for inclusion were adults aged 30 to 75 years diagnosed with T2DM according to the criteria established by the American Diabetes Association. Key exclusion criteria included a history of severe hypoglycemic events, any stage of renal disease, or proliferative retinopathy at the time of screening. Patients with a history of bariatric surgery or those on chronic steroid therapy were also excluded to maintain the integrity of the study's outcomes related to glycemic control.

Upon securing informed consent, a total of 1200 participants were enrolled based on power calculations designed to detect a minimal clinically significant difference in the primary outcome measures with a power of 90% and a significance level of 0.05. Baseline characteristics including age, duration of diabetes, body mass index (BMI), and existing treatment regimen were recorded.

Glycemic control was assessed using HbA1c levels measured quarterly throughout the study period. Additional laboratory tests included fasting blood glucose, lipid profile, and serum creatinine, among others, performed at six-month intervals. The development and progression of nephropathy were monitored through urinary albumin-to-creatinine ratio and estimated glomerular filtration rate (eGFR). Retinal assessments were conducted yearly using fundoscopy followed by digital retinal photography, interpreted by ophthalmologists blinded to the treatment regimens. Neuropathy status was evaluated using the Michigan Neuropathy Screening Instrument (MNSI) administered annually.

The data collection was facilitated through electronic medical records, complemented by patient self-reports during follow-up visits. Statistical analysis was planned using mixed models to accommodate the repeated measures design,

allowing for an assessment of both fixed and random effects of predictors on the outcome variables. Adjustments were made for potential confounders such as age, sex, duration of diabetes, and baseline medication use.

This rigorous methodology ensured that the study results would provide robust evidence to guide clinical decision-making regarding the management of glycemic control in patients with T2DM, aiming to mitigate the risk and progression of microvascular complications.

RESULTS

The prospective cohort study enrolled 1200 participants with Type 2 Diabetes Mellitus, predominantly males (60%) with an average age of 55 ± 10 years. The mean duration of diabetes at baseline was 8 ± 5 years, and the average Body Mass Index was noted as 30 ± 4 kg/m². Baseline glycemic control, indicated by a mean HbA1c of 7.5 ± 1.2% and fasting blood glucose of 150 ± 30 mg/dL, established the cohort's initial metabolic status.

Over the five-year study period, HbA1c levels showed a gradual decline, indicating an improvement in overall glycemic control. The mean HbA1c decreased from 7.5% at baseline to 6.8% by the end of the study, with the standard deviation narrowing from 1.2% to 0.8%, suggesting a convergence towards better glycemic management across the cohort.

The incidence of new microvascular complications was significant. Nephropathy was diagnosed in 15% of the participants (n=180), with a statistically significant increase noted (p=0.01). Retinopathy and neuropathy were even more prevalent, affecting 20% (n=240) and 25% (n=300) of the cohort, respectively, with p-values less than 0.001 for both complications, indicating a strong association with diabetes duration and initial poorer glycemic control.

The progression of existing microvascular complications was also noteworthy. Of those with worsening conditions, nephropathy, retinopathy, and neuropathy progressed in 60, 80, and 100 participants respectively. The respective p-values for the progression of these complications were 0.05, 0.02, and <0.001, demonstrating a significant worsening in patients with initially poor control.

Correlation analyses between glycemic control and microvascular complications revealed that better control was associated with reduced risks. The odds of nephropathy decreased by 15% for each 1% improvement in HbA1c (Odds Ratio [OR] = 0.85, 95% Confidence Interval [CI] = 0.75-0.95, p=0.01). Similar trends were observed for retinopathy (OR = 0.80, 95% CI = 0.70-0.92, p=0.002) and neuropathy (OR = 0.75, 95% CI = 0.65-0.87, p<0.001), underscoring the benefits of stringent glycemic control.

Subgroup analysis indicated that younger participants (age < 50 years) experienced a lesser reduction in risk for neuropathy compared to older participants (age ≥ 50 years) with the odds ratios being 0.85 (95% CI = 0.75-0.95, p=0.01) and 0.65 (95% CI = 0.55-0.77, p<0.001) respectively. This suggests that age may influence the protective effect of glycemic control against diabetes-related complications.

Multivariable analysis adjusted for potential confounders such as baseline BMI, sex, and treatment regimen further validated these findings. Adjusted odds ratios for the progression of nephropathy, retinopathy, and neuropathy were 0.88 (95% CI = 0.79-0.99, p=0.03), 0.82 (95% CI = 0.73-0.93, p=0.001), and 0.78 (95% CI = 0.69-0.89, p<0.001), respectively.

Sensitivity analyses, excluding participants who dropped out and using alternative definitions of microvascular complications, consistently showed similar patterns of association, supporting the robustness of the primary findings. For neuropathy, adjusted odds ratios remained significantly protective at 0.77 (95% CI = 0.67-0.89, p<0.001) and 0.79 (95% CI = 0.69-0.91, p<0.001) for each analysis respectively.

These results collectively suggest that improved glycemic control over time significantly correlates with reduced incidence and progression of microvascular complications in individuals with Type 2 Diabetes Mellitus, highlighting the critical role of effective diabetes management in preventing the debilitating effects of this disease.

Table 1: Baseline Characteristics of Participants

Variable	Total (n=1200)	Mean ± SD or n (%)
Age (years)		55 ± 10
Sex (male)	1200	720 (60%)
Duration of Diabetes (years)		8 ± 5
BMI (kg/m²)		30 ± 4
Baseline HbA1c (%)		7.5 ± 1.2

Fasting Blood Glucose (mg/dL)		150 ± 30

Table 2: Distribution of HbA1c Levels at Baseline and Follow-up

Time Point	Mean HbA1c (%)	Standard Deviation
Baseline	7.5	1.2
1 Year	7.2	1.1
2 Years	7.1	1.0
3 Years	7.0	0.9
4 Years	6.9	0.9
5 Years	6.8	0.8

Table 3: Incidence of Microvascular Complications

Complication Type	New Cases	Percent (%)	P-value
Nephropathy	180	15%	0.01
Retinopathy	240	20%	<0.001
Neuropathy	300	25%	<0.001

DISCUSSION

The findings from our study underscore the importance of effective glycemic control in mitigating the risk and progression of microvascular complications in individuals with Type 2 Diabetes Mellitus (T2DM). The observed decline in HbA1c levels over the study period and the associated reduction in the incidence of nephropathy, retinopathy, and neuropathy align with previous research demonstrating the benefits of glycemic control on microvascular outcomes[22].

Our results are consistent with those from the landmark United Kingdom Prospective Diabetes Study (UKPDS), which reported that each 1% reduction in HbA1c was associated with a 37% decrease in the risk of microvascular complications[23]. Similarly, our study found a significant reduction in the incidence of nephropathy and neuropathy with improved HbA1c levels, with odds ratios of 0.85 and 0.75 respectively, demonstrating a protective effect akin to that reported in the UKPDS.

Further, the ACCORD trial, which explored the effects of intensive versus standard glycemic control, revealed that intensive control did not significantly reduce the rate of advanced microvascular events over the median follow-up but did reduce the onset of albuminuria and some measures of eye complications[24]. In contrast, our study found notable reductions in both the onset and progression of all examined microvascular complications, including retinopathy and nephropathy, with respective odds ratios of 0.80 and 0.85.

The disparity between these findings may be attributed to differences in study populations, definitions of complications, or durations of follow-up. Moreover, the ADVANCE trial reinforced the necessity of individualizing glycemic targets, as overly aggressive control can lead to adverse outcomes [25]. Our findings echo this perspective, suggesting that while improving glycemic control is beneficial, it must be tailored to individual risk profiles and treatment tolerances to avoid potential hypoglycemia or other side effects.

The significant relationship between age and the protective effect of glycemic control on neuropathy found in our study highlights the role of age-related biological changes affecting diabetes management and complication risks. These results align with those from the DCCT/EDIC study, where younger participants exhibited more significant benefits from intensive glycemiccontrol [26]. This suggests that early and sustained intervention in glycemic management might yield long-term benefits in reducing the risk of microvascular complications, emphasizing the concept of 'metabolic memory'.

Despite these promising findings, our study has limitations inherent to observational designs, including potential confounding factors and selection bias. However, the robustness of our results is supported by sensitivity analyses that showed consistent associations under various assumptions.

Our study contributes to the growing body of evidence supporting the critical role of glycemic control in preventing microvascular complications in T2DM. Healthcare providers should consider these findings when designing and adjusting treatment plans for patients, promoting individualized approaches to achieve optimal glycemic targets and minimize the risk of complications.

CONCLUSION

The findings from this prospective cohort study highlight the significant impact of glycemic control on reducing the risk and progression of microvascular complications in individuals with Type 2 Diabetes Mellitus (T2DM).

Consistent with prior seminal studies like the UKPDS and ACCORD, our results demonstrate that improved HbA1c levels are strongly associated with lower incidences of nephropathy, retinopathy, and neuropathy. Specifically, each percentage point reduction in HbA1c was associated with substantial reductions in the odds of developing these complications—15% for nephropathy (OR = 0.85, 95% CI = 0.75-0.95, p=0.01) and 25% for neuropathy (OR = 0.75, 95% CI = 0.65-0.87, p<0.001). Moreover, the protective effects of better glycemic control were more pronounced in older adults, underscoring the need for early and individualized interventions to optimize diabetes outcomes. Healthcare providers should aim for personalized glycemic targets to prevent microvascular complications effectively while minimizing risks associated with overly aggressive glucose lowering. This study contributes valuable insights into the management of T2DM, encouraging ongoing efforts to refine therapeutic strategies and improve patient quality of life.

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