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Original Research Article

Evaluating the Effect of Oral Anticholinergics on Insulin Response in Impaired Glucose Tolerance: A Clinical Investigation

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Abstract:

Background: Impaired glucose tolerance (IGT) is a prediabetic state of suboptimal insulin secretion with increased insulin resistance. Anticholinergic drugs are widely prescribed for a range of conditions. They may impact glucose metabolism and the insulin response, which is of particular importance for the optimization of therapeutic strategies in IGT patients.

Objective: This study aimed to evaluate the effect of oral anticholinergic medications on the insulin response to an oral glucose load in patients with impaired glucose tolerance.

Methods: A prospective observational study on 120 patients diagnosed with IGT was performed from the outpatient department of Maa Vindhywasini Medical College, Uttar Pradesh, India from January 2022 to December 2022. The groups were divided into two types: ones taking oral anticholinergic therapy and a group that did not receive such therapy. An OGTT of 75 g was administered to all the participants, and plasma glucose and insulin levels were estimated at baseline, 30, 60, 90, and 120 minutes. Insulinogenic index and Homeostatic Model of Assessment-IR (HOMA-IR) were derived to determine beta-cell function as well as an index of sensitivity to insulin.

Results: The anticholinergics group presented a blunted insulin response to the oral glucose load; all the measured points of time showed lower values than the control group ($p < 0.05$). The insulinogenic index decreased by 25% in the group that received anticholinergics, pointing out reduced beta-cell function. HOMA-IR values were also higher in the group with anticholinergics, which suggested greater insulin resistance.

Conclusion: Oral anticholinergic drugs can impair insulin secretion and sensitivity in patients with impaired glucose tolerance. Patients at risk should be treated with caution, and glucose and insulin parameters monitored closely.

Keywords: Anticholinergics, Impaired Glucose Tolerance, Insulin Response, Oral Glucose Load, Insulin Resistance, Beta-Cell Function, Oral Glucose Tolerance Test

Introduction

Impaired glucose tolerance represents an intermediate state between normal glucose metabolism and type 2 diabetes mellitus. It is characterized by the postprandial glucose levels being raised and the suboptimal insulin response [1]. The stage is a critical one at which timely intervention can prevent or delay the progression to overt diabetes. The pathophysiology of IGT is a mixture of pancreatic beta-cell dysfunction and increased peripheral insulin resistance, each of which can be influenced by genetic, metabolic, and environmental factors [2]. Identification of factors that augment these abnormalities must be addressed in any effective management or prevention strategy. The mechanism by which all of these common medical conditions are addressed is that the drugs antagonize the effects of acetylcholine at muscarinic receptors [3]. Although generally effective in their clinical uses, new literature is beginning to raise questions about whether anticholinergic drugs might actually have deleterious effects on glucose metabolism [4]. One of the primary mechanisms through which acetylcholine exerts its effect on insulin secretion is by stimulation of muscarinic receptors on pancreatic beta cells [5]. By interfering with this pathway, anticholinergic drugs could impair insulin release, worsen hyperglycemia, and increase the risk of metabolic dysfunction in susceptible populations such as those with IGT [6].

Considering its potential importance, there is minimal research on how such anticholinergic drugs could affect glucose metabolism, especially on prediabetics. More than that, most studies existing in the medical literature are geared toward general

effects of these agents on metabolism with no specific findings regarding their insulin dynamics influence among IGT patients [7]. This is particularly worrisome because the prevalence of both IGT and anticholinergic use is high, especially among older adults who are already at an increased risk for metabolic disturbances [8].

This study thus bridges the existing gap by showing the effects of oral anticholinergic therapy on insulin responses to an oral glucose load among patients with impaired glucose tolerance. The studies will assess factors such as the plasma insulin levels, insulinogenic index, and insulin resistance using the HOMA-IR to illuminate the mechanistic link between altered glucose homeostasis and use of anticholinergics. The outcomes of the study could be extremely useful for clinical practice, informing physicians in the careful administration of anticholinergics to substantial risk groups and can help usher in targeted therapeutic approaches for IGT.

Methodology

This was a prospective observational study conducted over from January 2022 to December 2022 in the outpatient department of Maa Vindhywasini Medical College, Uttar Pradesh, India. The purpose of the study was to assess the effect of oral anticholinergic medications on the insulin response to an oral glucose load in patients with impaired glucose tolerance (IGT).

The study comprised 120 patients between the ages of 40 and 65 years diagnosed with IGT according to WHO criteria. Patients were recruited by stratified random sampling for an appropriate sample representation. The inclusion criteria included a fasting plasma glucose level between 100 and 125 mg/dL and/or 2-hour plasma glucose level between 140 and 199 mg/dL following a 75-g OGTT. Patients with at least three months of oral anticholinergic therapy were assigned to the study group, and patients not taking anticholinergics were assigned to the control group. The exclusion criteria included history of type 2 diabetes mellitus, pregnancy, severe hepatic or renal dysfunction, or medications that could affect glucose metabolism, such as corticosteroids or beta-blockers.

All participants underwent a 75-g OGTT. Plasma glucose and insulin levels were determined at baseline (fasting) and at 30, 60, 90, and 120 minutes after glucose ingestion. Blood samples were taken in fluoride and heparin tubes, centrifuged immediately, and analyzed for glucose by standardized enzymatic assays and for insulin by chemiluminescent immunoassays. Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR) formula, while beta-cell function was assessed using the insulinogenic index derived from the ratio of the change in insulin concentration to the change in glucose concentration during the first 30 minutes of the OGTT. Analysis was done on data using SPSS software (version 25.0). Mean ± SD of continuous variables, while categorical data as frequencies and percent were expressed. Independent t-test or the Mann-Whitney U test was done depending on distribution, for comparisons of glucose and insulin levels across distinct groups. Analysis of glucose and insulin level with more than two times involved repeated measures analysis of variance (ANOVA). Correlation analysis was done to observe the relationship of anticholinergic use with insulin-related parameters. A p-value of < 0.05 was considered statistically significant.

Subgroup analyses were also performed on the basis of age, gender, and dose of anticholinergic to investigate potential interactions of these factors with insulin response. The findings contribute to the better understanding of how oral anticholinergics affect glucose metabolism in IGT patients, which helps make more accurate clinical decisions regarding such a high-risk population.

Results

The total number of patients enrolled in the study was 120, divided into 60 in the anticholinergic group and 60 in the control group. The mean age of the participants was 53.2 ± 6.8 years, and there was a nearly equal representation of males and females. The baseline characteristics of both groups were comparable, with similar fasting glucose levels and BMI. Plasma glucose and insulin concentration at the time of the oral glucose tolerance test was significantly different between the two groups, with the anticholinergic group having a blunted response at every point in time. Key findings are summarised below in 10 tables.

Table 1 provides an overview of the demographic and baseline clinical characteristics of the participants.

Table 1: Demographic and Clinical Characteristics of Participants

Parameter	Anticholinergic Group	Control Group	p-value
Mean Age (years)	53.5 ± 7.1	52.8 ± 6.6	0.68
Male (%)	50% (30)	50% (30)	1.00
Female (%)	50% (30)	50% (30)	1.00
Mean BMI (kg/m²)	26.8 ± 3.5	26.5 ± 3.2	0.72
Fasting Plasma Glucose (mg/dL)	108.4 ± 7.5	107.9 ± 8.1	0.81

Table 2 shows plasma glucose levels at different time points during the OGTT.

Table 2: Plasma Glucose Levels During OGTT

Time Point (minutes)	Anticholinergic Group (mg/dL)	Control Group (mg/dL)	p-value
Fasting	108.4 ± 7.5	107.9 ± 8.1	0.81
30	156.7 ± 12.8	148.4 ± 13.5	0.04*
60	181.5 ± 15.2	169.3 ± 14.6	0.02*
90	174.6 ± 13.7	161.8 ± 14.0	0.01*
120	150.4 ± 12.3	140.8 ± 11.9	0.03*

Table 3 summarizes insulin levels at different time points during the OGTT.

Table 3: Plasma Insulin Levels During OGTT

Time Point (minutes)	Anticholinergic Group (µIU/mL)	Control Group (µIU/mL)	p-value
Fasting	12.3 ± 4.1	13.0 ± 3.8	0.52
30	42.5 ± 6.7	58.2 ± 7.3	<0.01**
60	68.3 ± 8.4	85.4 ± 8.9	<0.01**
90	55.6 ± 7.9	70.1 ± 8.5	<0.01**
120	34.2 ± 6.3	45.5 ± 6.7	<0.01**

Table 4 highlights the insulinogenic index, showing significantly reduced beta-cell function in the anticholinergic group.

Table 4: Insulinogenic Index

Group	Insulinogenic Index	p-value
Anticholinergic Group	0.82 ± 0.15	<0.01**
Control Group	1.10 ± 0.18	

Table 5 presents HOMA-IR values, indicating increased insulin resistance in the anticholinergic group.

Table 5: HOMA-IR Values

Group	HOMA-IR	p-value
Anticholinergic Group	3.25 ± 0.43	0.02*
Control Group	2.71 ± 0.38	

Table 6 categorizes patients based on their glycemic status post-OGTT.

Table 6: Glycemic Status Post-OGTT

Glycemic Status	Anticholinergic Group (%)	Control Group (%)	p-value
Normal Glucose Tolerance	10% (6)	20% (12)	0.21
Impaired Glucose Tolerance	90% (54)	80% (48)	0.18

Table 7 lists common anticholinergic medications used by the study participants.

Table 7: Anticholinergic Medications Used

Medication	Frequency (%)
Oxybutynin	40% (24)
Solifenacin	35% (21)
Tolterodine	25% (15)

Table 8 highlights the adverse effects reported by patients in the anticholinergic group.

Table 8: Adverse Effects of Anticholinergic Medications

Adverse Effect	Frequency (%)
Dry Mouth	60% (36)
Constipation	45% (27)

Blurred Vision	20% (12)

Table 9 shows the correlation between anticholinergic dosage and insulin response.

Table 9: Correlation Between Anticholinergic Dosage and Insulin Response

Dosage Level	Mean Insulin Response (µIU/mL)	p-value
Low	50.1 ± 6.2	<0.05*
Moderate	42.7 ± 5.9	<0.01**
High	35.6 ± 6.1	<0.01**

Table 10 evaluates the overall impact of anticholinergic therapy on insulin sensitivity and beta-cell function.

Table 10: Impact of Anticholinergic Therapy

Parameter	Anticholinergic Group	Control Group	p-value
Insulin Sensitivity (%)	Reduced by 18%	Reference	<0.01**
Beta-Cell Function (%)	Reduced by 25%	Reference	<0.01**

Discussion

This study provides valuable insights into the impact of oral anticholinergic medications on glucose metabolism and insulin dynamics in patients with impaired glucose tolerance (IGT). The findings demonstrate that anticholinergic therapy significantly alters the insulin response to an oral glucose load, highlighting the potential metabolic consequences of these medications in a high-risk population. The implications of these results extend to clinical practice, particularly in optimizing medication use for patients with prediabetic conditions [9].

One of the main outcomes identified is that the anticholinergic group had a blunted insulin response. The plasma insulin values at all time points for the OGTT were consistently lower in the anticholinergic group, coupled with a 25% reduction in the insulinogenic index, reflecting an impaired beta-cell function [10]. This might be mediated by the mechanism of action itself of the anticholinergics on the muscarinic receptors concerned in the cholinergic regulation of the secretion of insulin. A mechanism through which acetylcholine stimulates insulin release is by the activation of muscarinic receptors on pancreatic beta cells. Blockage of this pathway could theoretically dampen the insulinotropic effect of glucose; more importantly, it might cripple an already dysfunctional beta-cell pool from making enough insulin in response to a glucose load, which is a characteristic feature of IGT [11].

The study also showed increased insulin resistance in the anticholinergic group as shown by higher HOMA-IR values. Insulin resistance is a hallmark of prediabetes and T2DM, and its exacerbation in the presence of anticholinergic therapy raises important questions about the long-term metabolic risks associated with these drugs. A dose-response relationship between anticholinergic dosing and insulin resistance suggests that this is a dose-dependent adverse effect and warrants caution when anticholinergic agents are prescribed, particularly at higher doses [12].

Glycemic control, as defined by plasma glucose levels at points in time over the OGTT, was significantly worse within the anticholinergic group. At 30, 60, 90, and 120 minutes after glucose ingestion, plasma glucose was greater than that measured in the control group, thus showing poor glucose tolerance. Though there were no significant differences between groups for glycemic status following the OGTT, the trend of glucose metabolism deterioration within the anticholinergic group points to the importance of further research, especially within larger and longer-term studies [13].

The study also enumerates the demographic and clinical characteristics of the study participants. Older adults were overrepresented in the anticholinergic group, consistent with the common use of these drugs for many geriatric conditions, such as overactive bladder and gastrointestinal disorders. This raises concerns about the metabolic vulnerability of older adults to disturbances in glucose homeostasis induced by anticholinergic medications [14]. Other common side effects of anticholinergics include dry mouth and constipation, both of which could indirectly influence glucose regulation through the alteration of diet and gastrointestinal motility, although these were not specifically addressed in the study.

From drug-specific analysis, oxybutynin, solifenacin, and tolterodine were the most commonly used anticholinergics. Even though these drugs are generally well tolerated, their ability to affect glucose metabolism underlines the importance of personalized prescribing. Clinicians must balance the advantages of relief of symptoms with the risk of metabolic dysregulation, especially

in patients who already have pre-existing glucose intolerance or other metabolic risk factors [15].

This study has certain limitations despite its strengths, which include a well-defined cohort and robust methodology. The single-center design and relatively small sample size limit the generalizability of the findings. In addition, the study was conducted over a short duration, thus not allowing the evaluation of long-term metabolic outcomes. Future research should attempt to overcome these limitations by conducting multicentre, longitudinal studies on larger and more diverse populations. Further insights at the molecular level can also be drawn by studying the mechanisms through which anticholinergic-induced metabolic disturbances are mediated.

Conclusion

Oral anticholinergic agents greatly impair insulin secretion and enhance insulin resistance in patients with IGT. Such findings warrant the judicious prescription of anticholinergics for this high-risk population and meticulous monitoring of glucose and insulin measurements. Long-term metabolic risks related to anticholinergic therapy must be clarified further, and avenues to neutralize these adverse effects should be addressed.

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