

Pioglitazone and Insulin: Effects on Tight Glycaemic Control Assessed by the Continuous Glucose Monitoring System (CGMS)

A Monocentric, Parallel-Cohort Study

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Diabetes mellitus is accompanied by long-term microvascular, neurological, and macrovascular complications. These complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease, cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus. Prevention of these complications has been major goals of recent research.^[1]

Hyperglycaemia plays a key role in the pathogenesis of long-term complications of diabetes. Several studies have shown that improved blood glucose control, achieved by intensive therapy, results in a reduction of total mortality, diabetes-related endpoints, diabetes-related death and long-term complications of diabetes.^[1,2] In the DCCT (Diabetes Control and Complications Trial), intensive therapy designed to achieve blood glucose values as close to the normal range as possible with three or more daily insulin injections or treatment with an insulin pump resulted in a significant risk reduction for retinopathy, micro- and macroalbuminuria and clinical neuropathy compared to conventional therapy.^[1] However, a threshold of glycaemia for any type of complication for diabetes could not be determined.^[3]

There is clear evidence that glycosylated haemoglobin (HbA_{1c}) is the best parameter for assessing the quality of long-term glycaemic control in patients with type 2 diabetes.^[2-4] In the UKPDS (UK Prospective Diabetes Study), each percentage reduction in mean HbA_{1c} was associated with risk reductions of 21% for any endpoint related to diabetes, 21% for death related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications. Any reduction in HbA_{1c} is likely to reduce the risk of complications, with the lowest risk being related to HbA_{1c} values in the normal range (<6%).^[3] However, some patients develop microvascular disease despite acceptable HbA_{1c} levels.^[1] Thus, other features of glycaemic control, not reflected in the HbA_{1c}, might contribute to the risk of complications of diabetes. Importantly, postprandial hyperglycaemia is considered to be a significant risk factor for vascular complications, and thus provides additional information on the individual risk status.^[5-8] Indeed, a previous study has drawn attention to the importance of lowering post-prandial blood glucose for optimising overall glycaemic control and thus improving long-term outcomes in patients with type 2 diabetes.^[6]

In the DCCT study,^[1] hypoglycaemia was identified as the main severe adverse event associated with intensive therapy. The incidence of severe hypoglycaemia was approximately three times higher in the intensive therapy group than in the conventional therapy group.^[1]

The thiazolidinediones (also known as glitazones) are a new class of oral anti-hyperglycaemic agents. They are synthetic ligands that bond to the nuclear peroxisome proliferator-activated receptor (PPAR)- γ and exert their action by activating transcription of genes that, among others, regulate glucose and lipid metabolism as well as adipocyte differentiation and adipogenesis.^[9] At an average dose range of 15-45 mg/day, the thiazolidinedione pioglitazone, given as monotherapy or in combination with sulphonylureas, metformin or insulin, lowers HbA_{1c} by 0.3-1.7% and fasting blood glucose by 1.0-3.1 mmol/L from baseline after 12-26 weeks of treatment.^[9] Treatment with pioglitazone also resulted in a significant decrease in insulin resistance and improvement

of β -cell function in obese patients with type 2 diabetes.^[10] Besides achieving glycaemic control, pioglitazone provides improves the lipid profile.^[9] However, insulin therapy administered in multiple daily injections is believed to be the most potent regimen for achieving the best possible glycaemic control.^[11]

The Medtronic MiniMed[®] Continuous Glucose Monitoring System (CGMS) [Medtronic MiniMed, Northridge, CA, USA], a lightweight, portable, minimally invasive system, has recently been developed. CGMS is the first commercially available system that allows interstitial (tissue) glucose monitoring and determination of the prevalence of hypo- and hyperglycaemic episodes over time. The system provides a continuous glucose profile by taking samples from the subcutaneous fluid every 5 minutes for up to 3 consecutive days.^[12-14] A comparison between CGMS values and blood glucose measurements obtained by self-monitoring of blood glucose (SMBG) revealed that comparable measurements were obtained:

96,2% of the data pairs fell within the clinical acceptable regions (blood glucose values in zone A and B of the Clarke error grid analysis: zone A = clinical accurate within $\pm 20\%$ of reference values; zone B error greater than $\pm 20\%$ of reference values but with a benign effect or leading to no change of treatment).^[15] Differences in the prevalence of hypo- and hyperglycaemic episodes between different therapeutic approaches in well controlled type 2 diabetes patients can also be investigated using CGMS.

The aims of this study were to evaluate glucose profiles in patients with type 2 diabetes and compare the effects of insulin and Pioglitazone therapy on consistency of glucose levels over a 72-hour period (using CGMS).

1. Patients and Methods

A single-centre, parallel-cohort study was conducted to compare the effect of two treatment options - oral therapy with the thiazolidinedione pioglitazone and insulin therapy - on the prevalence of hypo- and hyperglycaemic episodes.

Patients with type 2 diabetes were recruited, if their HbA_{1c} was $\leq 7\%$. Thirty adult patients with well-controlled type 2 diabetes were included. Fifteen (seven men, eight women) were treated with pioglitazone 30mg once a day in combination with a mean dose of metformin 1700 mg/day; the other 15 (eight men, seven women) received a multiple-injection insulin therapy. Both groups were monitored for 72 h using the CGMS. This sensor system provided an average blood sugar measurement every five minutes (up to 864 readings in 72 h). In all patients, HbA_{1c} and fasting blood glucose (FBG) levels were determined at baseline. The number of hyper- and hypoglycaemic episodes in each group was recorded.

As this study had an exploratory design, the results have been analysed descriptively and no confirmatory statistical analysis method was used,

All patients provided written, informed consent to participate in the study. The study protocol was reviewed and approved by the ethics committee.

2. Results

Study participants were comparable regarding baseline characteristics. The mean ages of the pioglitazone and insulin groups were 58.7 and 63.5 years, respectively. The mean body mass index (BMI) was 32.7 kg/m² in the pioglitazone group compared with 31.5 kg/m² in the insulin therapy group. All patients had similar risk factors and co-morbidities. Figure 1 shows concomitant medication intake in both groups.

Baseline HbA_{1c} and FBG levels were 5.9 % / 120 mg/dL, respectively, in patients treated with pioglitazone compared with 6.4% and 131 mg/dL, respectively, in patients treated with insulin. A total of 844 glucose values were measured in the pioglitazone group, compares with 837 in the insulin group. During the study, seven hyperglycaemic episodes, defined as blood glucose concentrations of >160 mg/dL were detected in the pioglitazone group, compared with 16 in the insulin group. The mean duration of hyperglycaemic periods was

4.6 hours in patients receiving pioglitazone, compared with 11 hours in patients being treated with insulin. Three hypoglycaemic episodes (blood glucose <60 mg/dL) were recorded in patients receiving pioglitazone compared with seven hypoglycaemic episodes in the insulin group. The mean duration of hypoglycaemic periods was 0, 4 hours in patients treated with Pioglitazone compared with 1,9 hours in patients treated with multiple insulin therapy.

Ninety-two percent of patients treated with Pioglitazone and 78% of patients treated with insulin were in the glucose concentration range 60 to 160 mg/dL at all times throughout the 72-hour study period.

Baseline HbA_{1c} did not correlate with the frequency and duration of hyperglycaemic events. However, there was a positive correlation for hypoglycaemic episodes and insulin dose and a negative correlation for hypoglycaemic episodes and baseline HbA_{1c}.

3. Discussion

Various studies have suggested that HbA_{1c} is the best parameter for quantifying the risk of complications in patients with diabetes and for monitoring glycaemia.^[2-4] In our study, only well-controlled patients with close-to-normal HbA_{1c} were included. As shown in our study, even these well controlled patients exhibited a remarkable variability of glucose levels. This might explain the fact that even type 2 diabetes patients with near-normal HbA_{1c} levels develop micro- and macrovascular complications.^[1]

Our study used the CGMS, which allows reliable assessment of true glycaemic fluctuations over the 24-hour period and, almost non-invasively, the evaluation of hyper- and hypoglycaemic episodes.^[12-14] Seven hyperglycaemic episodes were identified in the pioglitazone group, compared with 16 in the insulin group. Interestingly, these episodes were independent from baseline HbA_{1c} values. This observation emphasises the advantage of continuous blood glucose monitoring in the management of type 2 diabetes patients. As shown in our study, hypo- and hyperglycaemic episodes can be detected only by continuous monitoring systems, which reveal a variability in blood glucose that is not identified by conventional finger-prick measurements. Importantly, preliminary studies have already shown that better management can be obtained if 24-h profiles of glucose concentrations are available.^[16] Our study also showed that CGMS can detect hypoglycaemic episodes, which is consistent with results from previous studies, in which this system was used.^[12,14] However, these previous studies investigated children with type 1 diabetes. In these patients, who were treated with a standard insulin regimen, a high prevalence and a large intra-individual variation in hypoglycaemia, particularly at night, were detected.

To our knowledge, the current study is the first to compare the effects of two treatment options on the prevalence of hyper- and hypoglycaemia in patients with Type 2 diabetes. We found a correlation between hypoglycaemic episodes and baseline HbA_{1c} as well as insulin dose; a previous study had already shown that the risk of severe hypoglycaemia increases continuously with lower HbA_{1c} values.^[1] The correlation between hypoglycaemic episodes and insulin dose is also in accordance with findings from a previous study.^[12]

Multiple insulin injections are believed to be the most effective way of achieving glycaemic control.^[11] Furthermore, a previous report suggested that more frequent postprandial glucose interventions by insulin injections was more important for improving metabolic outcome than the total insulin dose.^[6] In the current study, diabetic patients treated with pioglitazone experienced fewer episodes of hypo- and hyperglycaemia than patients treated with multiple insulin injections. In addition, the mean duration of hypo- and hyperglycaemic periods was shorter in patients receiving pioglitazone therapy.

Prospective studies have shown that in patients with type 2 diabetes, the risk of diabetic complications is strongly associated with previous hyperglycaemia. This association remains after adjustment for other known risk factors.^[3,17,18] Hyperglycaemia also plays a crucial role in the aetiology of small vessel disease and may explain the greater rate of

microvascular complications seen in a population with less satisfactory control of glycaemia.^[3] As a threshold of risk could not be detected, any improvement in glycaemic control across the diabetic range is likely to reduce the risk of diabetic complications.^[3] These data suggest that patients with type 2 diabetes benefit from drug treatment, which allow them to stay in the normoglycaemic range for as long as possible.

Pioglitazone has been shown in other studies to improve insulin resistance and provide sustained glycaemic control.^[19-21] Our study confirms the favourable effect of this new drug in patients with type 2 diabetes, including an ability to reduce hypo- and hyperglycaemic episodes and thereby reduce the risk of micro- and macrovascular complications.

4. Conclusion

On the basis of our findings in this study, we conclude that even well-controlled patients with type 2 diabetes show a remarkable variability of glucose excursions that is neither clinically obvious nor identified by current monitoring techniques. Continuous monitoring systems like the CGMS allow reliable assessment of hyper- and hypoglycaemic episodes that occur over the 24-hour period and are not identified by conventional finger-prick measurements.

Insulin therapy applied with multiple daily injections is still believed to be the most effective regimen for achieving the best possible glycaemic control.^[11] Currently, insulin treatment is introduced when glucose control can no longer be maintained with a combination of oral medications. However, the efficacy of oral treatment has increased as a result of the enhanced therapeutic effectiveness of new oral antidiabetic agents, which allow better control of blood glucose levels. In our study, we were able to show that, compared with insulin therapy administered via multiple daily injections, combination therapy with pioglitazone and metformin offered benefits in terms of lower prevalences of hypo- and hyperglycaemic episodes. Treatment with pioglitazone can be considered as providing reliable blood glucose control in the management of patients with type 2 diabetes.

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