Contribution of basal and postprandial hyperglycemia in type 2 diabetes subjects treated by an intensified insulin regimen : Impact of pump therapy in the OPT2MISE trial.

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Introduction

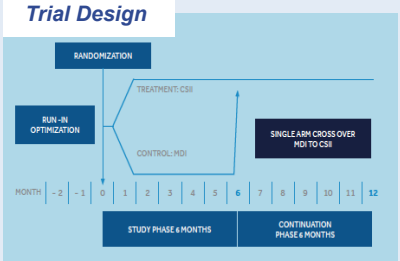
The relative contribution of fasting (FH) and postprandial hyperglycemia (PPH) in type 2 diabetes (T2D) is well documented in subjects treated by oral antihyperglycemic agents (1) and in subjects receiving one injection of a long-acting insulin analog (ie basal insulin therapy) (2). In contrast, The contribution of FH and PPH has not been well documented after intensification of insulin therapy with a multiple daily injection (MDI) regimen.

The OpT2mise study is the first large multicenter, randomized, controlled trial aiming to compare the efficacy and safety of pump therapy vs. MDI in insulin-using patients with T2D. CGM recordings performed in both conditions (MDI and pump therapy) gave us the opportunity to evaluate the respective contribution of FH and PPH observed when intensified insulin therapy with a basal-bolus regimen failed to obtain euglycemia in T2D subjects. Moreover, the effect of pump therapy on FH and PPH was also evaluated after switch to pump therapy during the trial. We also analyzed the predictive value of these variables on the metabolic response to pump therapy.

Materials and Methods

We performed an analysis of CGM recordings after 8-week run-in period in 259 MDI patients fenrolled in the OPT2MISE trial. Area under curve (AUC) HG was calculated in the basal (AUC-B), nocturnal (AUC-N) and postprandial (AUC-PP) periods according to baseline HbA1c level (Gr1 :<8, Gr2 :8-8.4, Gr3 :8.5-8.9, Gr4 :9-9.5, Gr5 :>9.5%). Changes were analyzed in 131 subjects switched from MDI to CSII. Analysis of variance was used for comparisons between groups.

Trial Design



Study Timeline & CGM analysis

Blinded Continuous Glucose Monitoring (CGM, iPro2, Medtronic) data was collected for a 6 day period before and 6 months after randomization and changes in glucose metrics were available in a subset from the study cohort.

AUC-B was calculated as the area above 100 mg/dl and below a line projected rightward for 24 hrs from the mean fasting glucose measured between 4am-7am.

AUC-N was calculated as the area above 100 mg/dl and below a line projected rightward from the mean nocturnal glucose measured between 0am-7am.

AUC-P was calculated as the ∑ (glucose values – basal threshold) when glucose values are > basal threshold, minus ∑ (basal threshold – glucose values) when glucose values are < basal threshold but > 100 mg/dl, or ∑ (basal threshold – 100) when glucose values are < 100 mg/dl. Total hyperglycemic exposure (AUC-T) resulted from the sum of AUC-B + AUC-P.

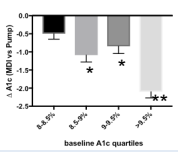
The relative contribution (RC) of fasting (FHRC) and postprandial hyperglycemia (PPHRC) were calculated according the formula : FHRC = AUC-B / (AUC-B+AUC-P), and the RC of PPH according the formula : PPRC= 1-FHRC.

Baseline Characteristics: Study Cohort vs OPT2MISE Cohort

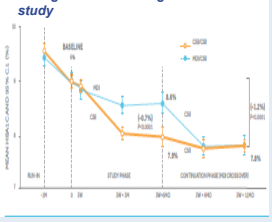
	Study cohort N=259	OPT2MISE cohort N=331	P Value
Age (Years)	56.5(9.70)	56.0 (9.60)	0.5177
Gender (Male/Female)(%)	142 (54.8%) /117 (45.2%)	180 (54.4%) / 151 (45.6%)	0.9141
Ethnic origin			0.2177
Caucasian	254 (98.1%)	318 (96.1%)	
Black African	5 (1.9%)	13 (3.9%)	
Duration of Diabetes (Year)	15.3 (8.03)	15.1 (7.96)	0.7576
A1C % (SD)	8.9 (0.81)	9.0 (0.75)	0.0893
Education N (%)			0.7519
Apprenticeship	45 (17.4%)	47 (14.2%)	
Secondary School	101 (39.0%)	136 (41.1%)	
College / University Degree	98 (37.8%)	130 (39.3%)	
Other	15 (5.8%)	18 (5.4%)	
Weight (kg)	96.5 (23.40)	96.1 (22.32)	0.8572
Body Mass Index (kg/m2)	33.6 (7.81)	33.4 (7.25)	0.7897
Metformin N(%)	183 (70.7)	232 (70.1)	0.8814
Insulin Dosage /kg	1.1 (0.43)	1.1 (0.42)	0.5132
Total Daily Insulin Dosage U (SD)	111.9 (52.46)	109.3 (51.66)	0.5437
Total dosage of Long-acting Insulin U (SD)	56.3 (29.44)	55.0 (29.78)	0.5886
Total dosage of Rapid-acting Insulin U(SD)	55.9 (32.35)	54.0 (31.35)	0.6668

Results

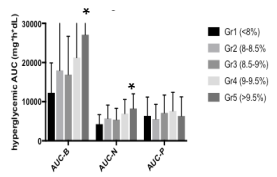
A1c Change after switch from MDI to Pump therapy among A1c quartiles



Changes in A1C throughout the study

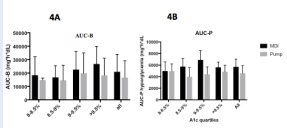


Hyperglycemic AUC among A1c quintiles in subjects on MDI regimen



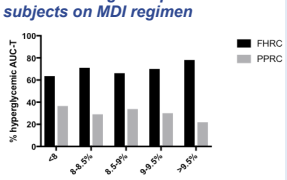
AUC-B increased significantly among baseline A1c quintiles (Gr 5 vs Gr4, p=0.01) (Gr5 vs Gr1, p = 0.0002). AUC-N also increased gradually among baseline A1c quintiles (Gr5 vs Gr4, p=0.05) (Gr 5 vs Gr1, p=0.0004) respectively. In contrast, AUC-P did not change significantly among baseline HbA1c quintiles from Gr 1 to Gr5 (p=0.100).

AUC-B and AUC-P on MDI and Pump therapy among A1c quartiles



When switching from MDI to pump therapy, both fasting and postprandial hyperglycemia decreased and the fasting To postprandial Hyperglycemia ratio remained rather stable. Nevertheless, AUC-B reduction was more pronounced in the highest A1c quartile (*, ≥9.5% vs <9.5%, p=0.0006). Similarly AUC-N reduction was deeper in the highest HbA1c quartile (p=0.0007) (data not shown). In contrast, AUC-P reduction was less pronounced in the highest A1c quartile (** ≥9.5% vs <9.5%, p=0.034).

Relative Contribution of FH and PPH according A1c quintiles in subjects on MDI regimen



FHRC was high across a range of A1c from <8% to ≥9.5% while PPRC was lower in the the highest A1c quintile (≥9.5%) compared to each lowest quintiles (<9.5%) (p=0.0036)

AUC hyperglycemic variables did not predict the metabolic response to pump therapy in the OPT2mise cohort

Hyperglycemic AUC variables were analyzed in 218 randomized patients who had CGM recordings at baseline and after 6-month pump therapy. Responders and non responders to pump therapy exhibited similar baseline variables ie AUC-B (20130±12769 vs 22176±12750 mg*h*dL^{-1}, p=0.25), AUC-N (6326±3629 vs 7083±3629 mg*h*dL^{-1}, p= 0.14), AUC-P(6395±4584 vs 6545±4244 mg*h*dL^{-1},p=0.81) and PPRC (28% vs 27.5%, p=0.72).

correlations	R	p
AUC-B vs A1c	0.31	0.0001
AUC-N vs A1c	0.32	0.0001
AUC-P vs A1c	0.08	0.2
FHRC vs A1c	0.14	0.0262
PHRC vs A1c	0.14	0.0262

Conclusions

1- Fasting and nocturnal Hyperglycemia are the major determinants of poor glycemic control in type 2 diabetes subjects with MDI failure. The main therapeutic goal is therefore to reduce nocturnal hyperglycemia which drives the subsequent daytime fasting hyperglycemia.

2- In the OPT2MISE trial, Both fasting and postprandial hyperglycemia were decreased by pump therapy resulting in a stable fasting/postmeal hyperglycemic ratio about 70%/30% before and after 6-month of pump utilization.

3- No AUC variable from baseline 6-day CGM was able to predict the metabolic response to pump therapy.

References

1) Monnier et al, Diabetes Care. 2007 Feb;30(2):263-9.

2) Riddle et all,. *Diabetes Care* 2011; 34: 2508-14.