An evaluation of postprandial glucose excursions in type 2 diabetic mellitus subjects on Monotard® HM (ge) versus Humulin N® or Humulin L® insulin, each in combination with metformin

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Abstract

Background

There is increasing evidence that postprandial hyperglycaemia is implicated in the development of macro- and microvascular diabetic complications. Thus, control of postprandial glucose levels (PPG), in addition to control of fasting blood glucose (FBG), will ensure overall glycaemic control in diabetic patients. This study evaluated the effectiveness of a current anti-diabetic regimen on PPG in patients with type 2 diabetes mellitus.

Method

A total of 31 type 2 diabetic subjects on combination treatment of either Humulin N® (HN), Monotard HM (ge)® (M) or Humulin L® (HL) insulin, with metformin, participated in a controlled, prospective, one-day visit study at a tertiary referral state diabetes clinic. The objective was to evaluate the effectiveness of the combination treatment of either M (n = 11) versus HN (n = 10) or HL (n = 10) insulin, each in combination with metformin, on PPG in this study cohort. Each subject was given a standardised meal after completing baseline procedures. Prescribed insulin doses were taken the night prior to the study day and metformin doses were taken with the standardised meal on the following morning, the study day. After completion of the meal, blood glucose levels were determined every half an hour at 0, 30, 60, 90, 120 and 150 minutes, thus providing a postprandial glucose profile for each subject. The data was analysed using ANOVA.

Results

The study cohort was South African, predominantly of Indian origin (54.8%), with a mean age of 59.2 ± 8 years, and 71% of the cohort was female. The subjects had a mean duration of diabetes of 11.4 ± 6.6 years, with 71% (n = 22) having a positive family history. The study cohort was obese (BMI 32.3 ± 6.2kg/m2, WHR 0.9 ± 0.1). A total of 61.3% (n = 19) of the study cohort was hypertensive, while 29% (n = 9) presented with at least one cardiovascular event and 48.3% (n = 15) had high total cholesterol. On entry to the study, the mean (± SD) FBG (10.3 ± 3.7mmol/l), fructosamine (369.9 ± 78.8mol/l) and glycosylated haemoglobin (9 ± 2%) were elevated. Each insulin group, HN, M and HL, was statistically matched for the above-mentioned and was therefore compared.

There was no statistically significant difference in the effectiveness of HN, M and HL, each in combination with metformin, on postprandial glucose levels (AUC glucose 0-150 minutes was 2100, 2212.5 and 2362.5mmol.min.l-1, per group respectively). Each insulin group presented with mean postprandial hyperglycaemia (PPH) at all time intervals (30, 60, 90, 120 and 150 minutes). Peak glucose levels were observed at 90 (16mmol/l), 90 (16.9mmol/l) and 60 minutes (17.6mmol/l) for HN, M and HL groups respectively. Since there was no statistically significant difference in PPH between and amongst the insulin groups at 60, 90 and 120 minutes, an approximation of PPG at 60 minutes would not adversely affect the determination of PPG compared to the recommended two hours. Within the HN, M and HL groups, a statistically significant difference in blood glucose levels was observed at 0 and 120 minutes (p = 0.003, 0.009 and 0.019 respectively). Groups with a higher FBG (at 0 minutes) had higher PPG (at 120 minutes), thus showing that the extent of FBG determines the degree of postprandial glycaemia.

Conclusion

In this study, HN, M and HL, each in combination with metformin, were not effective in controlling postprandial hyperglycaemia. HN was most effective in lowering the postprandial profile, although this was not statistically significant. The current treatment of the study cohort was also reviewed, as both FBG and PPG were not controlled. The use of a combination of short/rapid-acting insulin with a newly- formulated basal insulin is recommended, as both FBG and PPG should be treated to achieve overall glycaemic control.

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Introduction

Diabetes mellitus (DM) is a rapidly growing metabolic disorder of multiple aetiology. It is classified according to the American Diabetes Association (ADA) and World Health Organisation (WHO) into four aetiological categories, viz. type 1, type 2, diabetes due to other specific mechanisms or conditions, and gestational diabetes.[1]

Type 2 diabetes is one of the most common metabolic disorders and is now regarded as a worldwide epidemic, accounting for approximately 90% of all cases of diabetes.[2]

Type 2 DM is characterised by relative insulin deficiency and impaired insulin action. It generally forms part of the 'metabolic syndrome,' which comprises insulin resistance, obesity and a range of cardiovascular risk factors, such as dyslipidaemia and hypertension. Type 2 DM therefore poses a major therapeutic challenge, as it is involved in the pathogenesis of the specific macro- (cardiovascular events) and microvascular (nephropathy, retinopathy and neuropathy) complications of diabetes mellitus.[3]

The UK Prospective Diabetes Study (UKPDS 37) recently demonstrated that tight blood glucose control decreases the risk of micro- and macrovascular complications of DM.[4] Current measures of glycaemic control include FBG, glycosylated haemoglobin (HbA_{1c}) and fructosamine.

In type 2 DM, FBG is the main parameter of glucose metabolism that is used to monitor and control hyperglycaemia.[5] FBG informs the clinician of the patient's glycaemic status relative to the time at which the test was done. But it gives no indication of glucose exposure, toxicity or organ damage. HbA_{1c}, which is the gold standard in accessing glycaemic control, and fructosamine are both indices of long-term blood glucose control, as they estimate blood glucose during the preceding three months and two to three weeks respectively.[5]

However, it is estimated that 40 to 50% of individuals with type 2 diabetes are unaware that they have the disease, and that it may be undiagnosed for five to 10 years prior to clinical recognition.[6] Thus, recently-updated diagnostic criteria for diabetes have included tighter and more specific diagnostic tools, such as PPG. According to the WHO, PPH refers to blood glucose levels exceeding 11.1mmol/L two hours after a meal.[7]

PPH is an independent risk indicator for micro- and macrovascular complications, not only in type 2 DM, but also in those with impaired glucose tolerance.[8] Several studies, such as the Helsinki Policeman Study,[9] the Honolulu Heart Program[10] and the Islington Diabetes Survey,[11] have demonstrated a direct relationship between postprandial hyperglycaemia and cardiovascular complications. PPH is implicated in the development of cardiovascular disease through its harmful effects on the vasculature, carotid artery sclerosis and enhanced lipid peroxidation.[12]

The National Health and Nutrition Examination Survey found that patients who had PPH experienced a threefold increase in retinopathy, despite having normal fasting glucose levels.[13] Repeated exposure to postprandial hyperglycaemia can lead to β-cell dysfunction, which may become irreversible over time. This glucose toxicity induces a gradual, time-dependent establishment of irreversible damage to cellular components of insulin production and, therefore, to insulin content and secretion.[14]

The prevention and management of the complications of diabetes should therefore target both chronic and acute glucose fluctuations. While current diabetes treatment is focused on targeting FBG, the WHO and ADA recently included PPG in the metabolic assessment of type 2 DM.[7]

Objectives

The aim of this study was to evaluate postprandial glucose excursions in type 2 diabetes mellitus patients on M versus HL or HN insulin, each in combination with metformin. The primary objective of this study was to determine if the current anti-diabetic treatment of the study cohort controlled postprandial glucose levels.

Methods

All subjects were recruited from the Diabetes Unit at Addington Hospital, Kwa-Zulu-Natal. Thirty-one type 2 diabetic subjects were selected, based primarily on the metformin and basal insulin treatment used.

Subjects were grouped according to the basal insulin taken, i.e. HN (n = 10), M (n = 11) or HL (n = 10) insulin, each in combination with metformin. Insulin can be categorised into four principal types, namely short-acting, intermediate, long-acting and biphasic insulins, all of which are similar in their pharmacodynamic profiles, but differ in their pharmacokinetics. The insulins HN, M and HL, used in this study, belong to the intermediate basal insulin category. Intermediate insulin is divided into lente and NPH (neutral protamine hagedon) insulin, which have zinc and protamine ions respectively, and which are responsible for delaying absorption and extending the duration of action. HL and M are lente insulins (duration of action is 22 to 24 hours), whilst HN is an NPH insulin (duration of action is 18 to 24 hours).[15]

This controlled, prospective study required a one-day visit per subject. On the study day, the subjects were required to come to the clinic fasting. The subjects continued with their concurrent medication and_were required to maintain their current drug regimens by taking the insulin (HN, M or HL) dose at bedtime and the metformin doses, in divided doses, as prescribed. The baseline determinations included blood pressure readings and weight, height, hip and waist measurements. Blood samples were collected for biochemical measures: full blood count (FBC), urea and electrolytes (U&E), lipid profile, liver function tests (LFT) and glycaemic measures (fructosamine, HbA_{1c} and FBG values).

Figure 1: Illustration of the timeline of the study

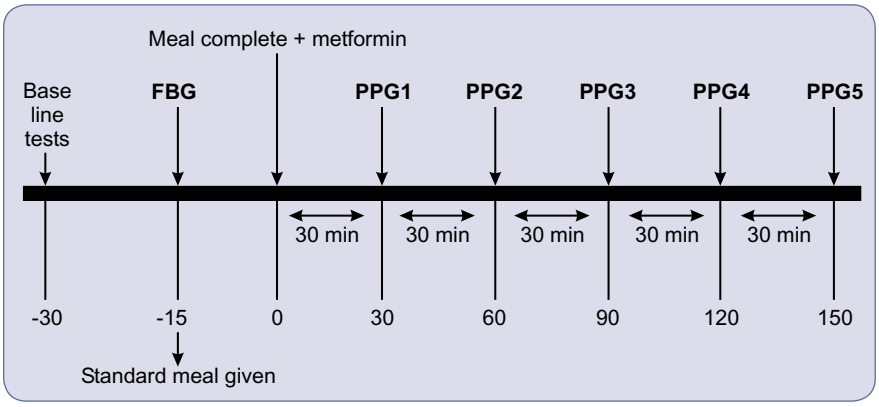


Table I: Comparison of mean ± SD of parameters for Humulin N® (HN), Monotard (M) ® and Humulin L® (HL) groups

PARAMETER	HN (n = 10)	M (n = 11)	HL (n = 10)	*p* VALUE*
Age (years)	57.6 ± 6.5	59.2 ± 10.7	60.7 ± 6.3	0.703
Duration of DM (years)	12.3 ± 8.3	11.6 ± 5.9	10.3 ± 5.9	0.796
Total daily insulin dose (iu)	36.1 ± 17.7	37.6 ± 14.3	34.5 ± 11.9	0.89
Total daily metformin dose (mg)	1710 ± 443	1886 ± 661.1	1920 ± 542.2	0.67
HDL:LDL ratio	0.34 ± 0.09	0.31 ± 0.07	0.28 ± 0.1	0.341
Urea (mmol/L)	4.9 ± 1.9	5.7 ± 2.3	4.6 ± 1.9	0.417
Creatinine (μmol/L)	73.9 ± 10.8	97.7 ± 30.9	100 ± 40.5	0.113
FBG (mmol/L)	9.2 ± 2.08	10.5 ± 4.7	11.5 ± 4.2	0.430
Fructosamine (μmol/L)	371.5 ± 78.8	360.4 ± 79.9	378.7 ± 84.8	0.873
HbA_{1c} (%)	8.3 ± 1.5	9 ± 2.1	9.8 ± 2.2	0.296

**p* values > 0.05 indicate no differences between group means
The mean +/- SD blood glucose level at each time point (see table 2) was above the recommened 11.1 mmol/l, indicating that the study cohort had postprandial hyperglycaemia'

Prescribed insulin doses were taken the night prior to the study day and metformin doses were taken with the standardised meal the following morning, on the study day. Subjects consumed a standardised meal (carbohydrate content of 55.9 g, protein of 13.6 g and fat of 12.4 g) to completion over a 15-minute period in the presence of the researcher.

After completion of the meal, blood glucose levels were determined within the allocated time (using the glucose oxidase method) every half an hour at 0, 30, 60, 90, 120 and 150 minutes, thus providing a postprandial glucose profile for each subject (see Figure 1).

The data was analysed using ANOVA. The null hypothesis for this study states that there is no difference in the means of the three groups for a specific parameter. If the *p* value is > 0.05, the null hypothesis is accepted. All data are reported as means [± standard deviation (SD)] and statistical significance was defined as $p < 0.05$.

Results

The study cohort was South African, predominantly of Indian origin (54.8%), was aged 59.2 ± 8 years and 71% were females. The subjects had a mean duration of diabetes of 11.4 ± 6.6 years, with 71% (n = 22) having a positive family history.

The study cohort was obese (body mass index (BMI) 32.3 ± 6.2kg/m^2, waist-hip ratio (WHR) 0.9 ± 0.1). A total of 61.3% (n = 19) of the study cohort were hypertensive, while 29% (n = 9) presented with at least one cardiovascular event and 48.3% (n = 15) had high total cholesterol. Drug history included 32.3% (n = 10) on ACE inhibitors, 32.3% (n = 10) on low-dose diuretics, 29% (n = 9) on calcium antagonists, 19.4% (n = 6) were on β-blockers, and 0% (n = 0) on cholesterol-lowering drugs. The mean FBC, U&E and LFT for the study population were within the normal laboratory range, except for globulin levels, which were elevated in 90% (n = 28) of the study population.

Each insulin group, HN, M and HL, was statistically matched for parameters, as per Table I. It was therefore possible to make comparisons between and among the groups.

On closer inspection (see Table III), HN showed the largest, but not statistically significant, decrease in postprandial glucose levels (lowest $AUC_{\text{glucose 0-150 minutes}}$).

*Peak glucose levels were observed at 90 (16 mmol/L), 90 (16.9 mmol/L) and 60 minutes (17.6 mmol/L) for the HN, M and HL groups respectively. Since there was no statistically significant difference in PPH between and among the insulin groups at 60, 90 and 120 minutes, an approximation of PPG at 60 minutes would not adversely affect the determination of PPG, compared to the recommended two hours. This is of particular importance in busy clinical settings.

Within the HN, M and HL groups, a statistically significant difference in blood glucose levels was observed at 0 and 120 minutes (p = 0.003, 0.009 and 0.019 respectively). The HN, M and HL groups presented with mean fasting hyperglycaemia at 0 minutes of 9.1 ± 2.2, 9.3 ± 3.7 and 11.5 ± 3.6 mmol/L respectively and a mean postprandial hyperglycaemia at 120 minutes of 15.3 ± 3.7; 15.7 ± 4.1 and 16.3 ± 4.7 mmol/L respectively. Groups with a higher FBG (at 0 minutes) presented with higher PPG (at 120 minutes), thus indicating that the extent of FBG determines the degree of postprandial glycaemia.

Discussion and conclusion

In this study, ADA and WHO criteria were used to define fasting hyperglycaemia as blood glucose levels ≥ 7

Table II: Comparison of mean (± SD) blood glucose profiles between insulin groups

PARAMETER (mmol/L)	HN	M	HL	*p* VALUE*
Ave FBG at 0 min	9.1 ± 2.2	9.3 ± 3.7	11.5 ± 3.6	0.200
Ave PPG at 30 min	13.3 ± 2.5	14.9 ± 3.3	16.2 ± 4.3	0.171
Ave PPG at 60 min	15.5 ± 3.6	16.8 ± 3	17.6 ± 4.7	0.471
Ave PPG at 90 min	16 ± 4	16.9 ± 3.7	17.6 ± 4.2	0.674
Ave PPG at 120 min	15.3 ± 3.7	15.7 ± 4.1	16.3 ± 4.7	0.869
Ave PPG at 150 min	14 ± 3.6	14.1 ± 4.2	14.8 ± 4.7	0.898

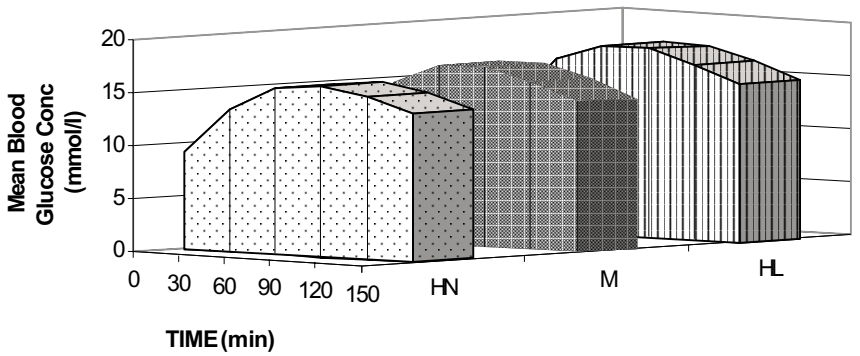
**p* values > 0.05 indicate no differences between group means
There was no statistically significant difference in the effectiveness of HN, M and HL, each in combination with metformin, on postprandial glucose levels (see Figure 2).

Table III: Change of mean glucose area under the curve per time interval per insulin group

PARAMETERS	AUC_{0-30} mmol.min.l^{-1}	AUC_{0-60} mmol.min.l^{-1}	AUC_{0-90} mmol.min.l^{-1}	AUC_{0-120} mmol.min.l^{-1}	AUC_{0-150} mmol.min.l^{-1}
HN	330	750	1207.5	1665	2100
M	360	817.5	1305	1777.5	2212.5
HL	397.5	892.5	1410	1905	2362.5
p Values*	0.198	0.376	0.378	0.231	0.264

p values > 0.05 indicate no differences between insulin groups per time interval
This decrease in postprandial glucose level was followed by M and then HL, which showed the smallest reduction (highest AUC values)'

Figure 2. Mean glucose concentration vs. time, showing AUC $_{0\text{-}150}$ (shaded area) for each insulin type



mmol/L, and the WHO criteria were used to define two-hour postprandial hyperglycaemia as blood glucose levels ≥ 11.1 mmol/L after a meal.[7]

The high mean ± SD FBG, HbA_{1c} and fructosamine levels of the total study cohort showed the poor status of glycaemic control in the subjects, not only on entry into the study, but also over the previous months. As glycaemic measures were high on entry, the study cohort was already at a high risk for diabetic complications.

The mean age, duration and positive history of diabetes, and the classification of the subjects as obese, all increased the risk of diabetic complications in the study cohort. To further increase the progression of macrovascular complications, particularly the risk of cardiovascular events, the study cohort was not on any prophylactic cholesterol-lowering agents, while only 16.1% were on aspirin. Also, 61.3% presented with hypertension and 48.3% presented with high total cholesterol levels. Thus, the treatment of hyperglycaemia alone, without other prophylactic measures, is not likely to succeed in decreasing long-term complications of diabetes mellitus.

In this study, the diabetic treatment comprised metformin combined with a basal insulin. UKPDS (1977–1999) demonstrated that only 50% of normal β-cell function remains by the time type 2 diabetes is diagnosed, and that this function continues to deteriorate over time, despite treatment.[15] Thus, combination therapy becomes a safer and more convenient option by combining two agents with different modes of action to produce a synergistic therapeutic effect. The metformin and insulin combination in this study cohort is logical, as insulin resistance is targeted directly.[16] Metformin reduces FBG and PPG by stimulating glycolysis in peripheral tissues, reducing hepatic gluconeogenesis and improving insulin resistance and sensitivity; whilst insulin suppresses the increased hepatic glucose production and lowers FBG concentrations.[17]

However, in this study, the current treatment (HN, M or HL, each in combination with metformin) was shown to be ineffective in controlling postprandial glycaemia with respect to the following parameters: mean two-hour postprandial glucose concentration at 120 minutes and AUC $_{\text{glucose 0-150 minutes}}$.

All insulins are similar in their pharmacodynamic profiles, but differ in their pharmacokinetics. As HN, M and HL are pharmacologically classified as human basal insulins, they consequently showed similar effects on the postprandial glucodynamic parameters. This study found no statistically significant differences in the mean postprandial glucose concentrations among the three insulins groups, each in combination with metformin at each time point, namely 0, 30, 60, 90, 120 and 150 minutes.

However, on closer inspection, the postprandial glucose-lowering effect of the HN group was consistent with lower glucose concentration values from baseline, for all time intervals, for the AUC $_{\text{glucose 0-150 minutes}}$, compared to the M and HL groups (not statistically significant).

This variability of the insulin responsiveness may be attributed to the different pharmacokinetic characteristics of insulin. Compared to the lente insulins (M and HL), the onset of action of neutral protamine hagedorn (NPH) insulin (HN) is quicker.[15] The early peak of HN was confirmed by Bilo, who showed that, after the administration of NPH insulins, an earlier rise of plasma insulin levels was observed, compared to the gradual increase of plasma insulin levels after the administration of zinc insulins.[18] Hence the pharmacokinetic differences of the insulins resulted in the pharmacodynamic differences seen in this study.

This largest postprandial glucose reduction (not statistically significant) in the HN group was also influenced by the better glycaemic control of the group on entry, compared to the M and HL groups (Table I). Although not statistically significant, the HN group presented with the youngest group, the highest glycaemic control on entry and showed the lowest risk for cardiovascular disease (highest HDL:LDL ratio) and renal impairment (lowest creatinine levels), compared to the M and HL groups.

In conclusion, the current treatment of the study cohort was reviewed, as both FBG and PPG were not controlled due to the progressively worsening hyperglycaemia of type 2 diabetes. The study cohort's current treatment of combining oral medications with an intermediate to long-acting insulin as a twice-a-day or single-dose bedtime regimen, was logical, as it did aim to control overall glycaemia and weight gain. The rationale for the use of the study cohort's current treatment is that insulin, by suppressing hepatic glucose output during the night, will control the fasting blood glucose, while the oral medication(s) continues to control postprandial glucose levels and glucose throughout the day. However, as discussed above, the study cohort's glycaemia was uncontrolled. As diabetes mellitus is a progressive disease, treatment should be intensified as the disease progresses. Hence, in this study cohort, the current treatment should be reviewed to target the fasting and postprandial hyperglycaemia.

Any further dosage adjustments of the basal insulin doses would not be any more beneficial than the current treatment in this study cohort. Rather, the effect of twice-a-day versus a single bedtime insulin dose on FBG or PPG levels should be investigated further. In addition, a further increase in the metformin doses needs to be evaluated, as impaired renal function and the development of lactic acidosis should first be investigated in this study cohort. The substitution of metformin with other oral agents (e.g. α-glucosidase inhibitors, meglitinide or thiazolidinediones) may

improve glycaemic control by targeting both FBG and PPG, but the extent of this control is limited by the decline in beta cell response, which is common as the disease progresses. Thus, as DM is a disease that progresses with age, the addition of other hypoglycaemic agents (i.e. short-acting insulins) that target postprandial hyperglycaemia to the current treatment would be most beneficial and cost effective. The use of a combination of short/rapid-acting insulin with a newly-formulated basal/long-acting insulin (such as insulin glargine) is recommended, as both FBG and PPG should be treated to achieve overall glycaemic control.

This study also showed that the extent of fasting hyperglycaemia determines the degree of postprandial hyperglycaemia, and thus should be monitored. An approximation of PPG at one hour, as opposed to two hours, will not impact on the interpretation of glucose levels postprandially, as this study showed no statistically significant differences between PPG levels at 60, 90 and 120 minutes. This would benefit busy clinical settings.

Evidence shows that targeting FBG is more beneficial when HbA_{1c} and fructosamine values are very high, whereas targeting PPG is more effective when HbA_{1c} and fructosamine values are lower.[19] As FBG improves, the PPG contribution to glycaemic control dominates, and when HbA_{1c} values decrease to 7%, the PPG contribution increases to about 70%.[19] This study therefore recommends that postprandial glucose measurements should have an **equal place** with fasting glucose measurements in the management of type 2 DM to achieve overall glycaemic control and hence prevent diabetic complications.

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