Katte et al. Int J Diabetes Clin Res 2016, 3:056
Volume 3 | Issue 2
ISSN: 2377-3634

International Journal of
Diabetes and Clinical Research

Research Article: Open Access

The Effects of a One-week Short Intensive Insulin Intervention on Insulin Sensitivity in Patients with Poorly Controlled Type 2 Diabetes

Jean-Claude Katte[1]*, Eugene Sobngwi[2,3,4], Vicky Kamwa[4], Mesmin Y Dehayem[2,4], Jean-Louis Nguewa[5], Andre-Pascal Kengne[6,7] and Jean Claude Mbanya[2,4,8]

[1]Bafoussam Regional Hospital, Diabetes and Hypertension Treatment Center, Bafoussam, Cameroon

[2]Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon

[3]Laboratory for Molecular Medicine and Metabolism, Biotechnology Center, University of Yaoundé I, Yaoundé, Cameroon

[4]National Obesity Center, Yaoundé Central Hospital, Yaoundé, Cameroon

[5]Endocrinologie et Diabétologie, Hôpital Lariboisière, Paris, France

[6]Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

[7]Non-Communicable Disease Research Unit, South African Medical Research Council, South Africa

[8]Biotechnology Centre, University of Yaoundé I, Yaoundé, Cameroon

***Corresponding author:** *Jean-Claude Katte, Bafoussam Regional Hospital, Diabetes and Hypertension Treatment Center, Bafoussam, Cameroon, E-mail: jckatte@gmail.com*

Abstract

A 3-4 week of intensive insulin intervention corrects hyperglycemia, improves insulin secretion, glycemic control, and insulin sensitivity in people with type 2 diabetes mellitus. We assessed the effect of a shorter course of intensive insulin therapy on insulin sensitivity in people with T2DM. Fifteen poorly controlled subjects with severe hyperglycemia were hospitalized and treated with intensive insulin therapy for 7 days. The short insulin tolerance test was performed before and after the insulin intervention. The intervention consisted of a 24-hour intravenous rapid-acting insulin via electric pump followed by multiple daily insulin injection for six days. This study was registered with the National Ethics Committee Ref. N°233/CNE/SE/2010. Fasting glycemia dropped from 385.4 to 134.4 mg/dL. Insulin sensitivity improved significantly after the insulin intervention (1.98 %/min vs. 2.26 %/min; $p < 0.001$). Total and LDL cholesterol (both $p < 0.001$) significantly decreased while changes in HDL-cholesterol and triglycerides were not significant. Body mass index increased from 26.4 to 27.0 kg/m2 ($p = 0.03$), fat mass from 23.1 to 28.2 ($p < 0.001$) and fat free mass from 50.2 to 54.0 kg ($p < 0.001$).These results demonstrate that in poorly controlled type 2 diabetes with severe fasting glycemia, a one week course of intensive insulin intervention can improve insulin sensitivity and successfully alleviate glucotoxicity and lipotoxicity.

Key words

Fasting blood glucose, Diabetes, Insulin sensitivity, Intensive insulin intervention

Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia and disturbance of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. The main pathophysiological defect responsible for the development of hyperglycemia in type 2 diabetes are decreased insulin sensitivity (insulin resistance) and impaired insulin secretion [2,3]. The continuous insulin resistance leads to progressive loss of β-cell function, consequential chronic hyperglycemia and the detrimental effects which are known as "glucotoxicity" [4]. Chronic excess lipids concentration also contributes to the progressive decline in β-cell function through "lipotoxicity" [5,6].

Research in animal models and human subjects with diabetes has led some researchers to suggest that glucose toxicity contributes both to insulin resistance and β-cell impairment seen in type 2 diabetes [7]. Consequently, insulin resistance and β-cell dysfunction are reinforced in patients with hyperglycemia and especially those with chronic severe hyperglycemia. Therefore stringent control measures aimed at improving chronically elevated blood glucose levels may help alleviating the cellular "toxic" effect of hyperglycemia [8]. Growing evidence suggests that insulin therapy can help correct the underlying pathogenic mechanisms of type 2 diabetes [9]. Several reports have also shown that short-term intensive insulin therapy can induce long-term glycemic control in type 2 diabetic patients with hyperglycemia. In this line, *Garvey et al.* [10] showed that a 3-week continuous subcutaneous insulin infusion (CSII) in 14 poorly

ClinMed International Library

Citation: Jean-Claude K, Sobngwi E, Kamwa V, Dehayem MY, Jean-Louis N, et al. (2016) The Effects of a One-week Short Intensive Insulin Intervention on Insulin Sensitivity in Patients with Poorly Controlled Type 2 Diabetes. Int J Diabetes Clin Res 3:056

Received: November 04, 2015: **Accepted:** May 09, 2016: **Published:** May 12, 2016

Table 1: Insulin infusion Protocol.

Capillary glycemia (mg/dL)	Insulin infusion dose (mL/h)	Adjustment made with respect to meals
80-120 mg/dL	1 mL/h	15 minutes before meals, add 5IU to the current insulin dose and allow to flow for 2 hours. Measure the glycemia after these 2 hours and adjust according to the protocol. Note: 1 IU = 1 mL
121-150 mg/dL	2 mL/h	
151-200 mg/dL	3 mL/h	
201-250 mg/dL	4 mL/h	
251-300 mg/dL	5 mL/h	
301-400 mg/dL	7 mL/h	
> 400 mg/dL	10 mL/h	

controlled type 2 diabetic patients significantly improved insulin secretion. This was later confirmed by *Ryan et al.* [11] in 16 newly diagnosed type 2 diabetic patients treated for 2-3 weeks.

Many studies have elucidated the effects of insulin therapy on β-cell function and insulin secretion, but evidence is sparse on the effect of insulin therapy on insulin sensitivity and especially in the context of short term intensive insulin therapy. We therefore postulated that one-week intensive insulin intervention in poorly controlled type 2 diabetic patients with severe hyperglycemia would improve insulin sensitivity. This present experimental study aims to assess the effects of one week intensive insulin intervention on insulin sensitivity in patients with type 2 diabetes.

Materials and Methods

A prospective clinical trial using a before and after design, where each subject was his own control was carried out at the Diabetes and Metabolic Disease Unit of the Yaoundé Central Hospital, Cameroon. The study unit has been described previously [12]. The study population consisted of 15 subjects with poorly-controlled type 2 diabetes defined as the combined fasting capillary glucose ≥ 300 mg/dL and A1C ≥ 8%. After obtaining informed consent, all the subjects were admitted for the duration of the study. They were clinically euthyroid and without evidence of renal, hepatic, or cardiac dysfunction. No subject had an intercurrent disease. The study was approved by the National Ethics Committee of Cameroon with registration number: N°233/CNE/SE/2010.

Study Procedures

Upon admission, all participants were started on an isocaloric diet maintained throughout on a 2200 calories/day, comprising 60% of carbohydrate**.** The proportion of total carbohydrate was estimated by carbohydrate counting. After an overnight fast, blood samples were drawn for blood urea nitrogen, creatinine and lipid profile.

The short insulin tolerance test was performed over a period of 15 minutes using a bolus dose of insulin of 0.15 IU/kg body weight. To be able to classify the patients according to their insulin sensitivity, we set our definition of insulin resistant state as a KITT value < 2.5%/minute, according to a previous study [13]. After the short insulin tolerance test, a 20 G catheter equipped with a 3-way connector was inserted retrogradely into one ante-cubital vein for insulin and glucose infusion. An extension line was connected at one end of the 3-way connector to a 50 mL syringe containing a rapid-acting insulin (Actrapid® HM Novo Nordisk A/S 2880 Bagsvaerd, Denmark), and adapted to a calibrated electric pump (ALARIS® MEDICAL SYSTEMS London, UK Ltd). Vessel blockage was prevented by a slow and constant infusion of 42 mL per hour of 0.9% saline solution flowing via a 15 µm tubular filter connected to the other end of the 3-way connector and onto a calibrated electric volumetric pump device (IVAC Corporation-Volumetric Pump Model 598, San Diego-California, USA).

Insulin infusion

The insulin infusion was prepared in isotonic saline solution; 50 IU of the soluble human insulin (Actrapid®) was diluted, in absolute sterile conditions. In a 50 mL syringe, the insulin was made up to the 50 mL mark with 0.9% saline solution. The syringe was then adapted into the calibrated electric pump and connected to the 3-way tap via the extension line. Insulin infusion was started at the minimum dose of 1 IU/hour and was adjusted 1 hour later based on the capillary glycemia, according to a sliding scale insulin infusion algorithm (Table 1). Capillary glycaemia was monitored every hour using a portable glucose meter (ONE TOUCH®) for the first 24 hours. The blood pressure and the pulse were also monitored every hour, including monitoring for signs of hypoglycemia. The insulin infusion was continued for 24 hours and permitted the calculation of the total daily insulin requirements of the individual patients.

Insulin treatment

The insulin treatment was continued after 24 hours using a multiple daily insulin (MDI) injection protocol based on the total insulin requirement calculated for each individual patient. The total insulin requirements for each patient was estimated using the insulin infusion via the electric pump and was converted into subcutaneous insulin injections [14]. Soluble human insulin (Actrapid®) and pre-mixed insulin (Mixtard 30®) were used in the following proportions: 30% of pre-meal Actrapid® at 7:00 a.m., 40% of Actrapid® at 1:00 p.m. and 30% of Mixtard® 30 at 7: 00 p.m. The MDI protocol treatment was to target fasting capillary glycemia between 70 - 140 mg/dL and capillary glycemia at 2 hours after each three meals of less than 180 mg/dL. The doses of insulin administered were titrated every day in order to attain the glycemic goal. The MDI treatment protocol was maintained for the next 6 days. On the next day, blood samples were again drawn for biochemical analyses.

Analytic methods

Capillary blood glucose was measured using a glucose oxidase method (ONE TOUCH®, Milpitas, CA, USA); which is a quantitative measurement of glucose in whole blood. The lipid profile was measured using a colorimetric method implemented with an automatic machine (UV-VIS SPECTROPHOTOMETER: UV mini 1240, SHIMADZU). Creatinine was measured using the Creatinine-Direct (Deiminase - UV) reagent and blood urea nitrogen using the UREA COLOR - Urease Berthelot Test. Urine Glucose and Urine Proteins were measured using a dipstick (CYBOW™, DFI Co., Ltd, Gyung-Nam, Korea) and expressed in mg/dL and A1C using the High Performance Liquid Chromatography method (HPLC) by an automatic BIO RAD D-10 machine.

Outcomes and adverse events

The main study outcomes were any changes in fasting capillary glucose, and insulin sensitivity. Other outcomes included changes in lipid profile and anthropometric measurements, compared before and after the insulin intervention. Expected adverse events were hypoglycemia and local reaction at the site of infusion, which were monitored for, as well as unpredictable events.

Data analysis

Data was analyzed using SPSS for Windows® Version 17. Results are presented as frequencies or mean and standard deviation. Paired sample t-test was used to compare values obtained before and after intensive insulin intervention. Correlations were done using the Pearson's rank correlation test. The Student t-test was used to compare characteristics between men and women and their mean insulin sensitivity values. A p-value less than 0.05 was considered statistically significant for all analyses.

Results

All 15 subjects tolerated the short insulin tolerance test and the insulin intervention well. No severe hypoglycaemic reactions were recorded. Before the insulin intervention, all the subjects exhibited symptoms of poor glycemic control such as frequent urination and thirst and fatigue as evidenced by the mean fasting capillary glucose level of 385.4 ± 98.6 mg/dL, and mean A1C level of 12.9 ± 2.3%. Symptoms of diabetes resolved shortly after insulin intervention was started.

There was a significant difference in the percent body fat ($p = 0.002$) and the fat free mass ($p = 0.02$) between the male and female

Table 2: Anthropometric and clinical data at baseline evaluation.

Characteristics	Total	Male	Female	p-value
Number of subjects (n)	15	7	8	
Systolic blood pressure (mmHg)	119.6 ± 12.6	120.4 ± 14.1	118.8 ± 12.2	0.82
Diastolic blood pressure (mmHg)	74.1 ± 8.4	77.1 ± 8.1	71.3 ± 8.1	0.19
Weight (Kg)	73.3 ± 14.1	77.0 ± 18.7	70.1 ± 8.5	0.36
Body mass index (Kg/m^2)	26.4 ± 3.9	26.9 ± 11.3	25.8 ± 3.8	0.62
Waist circumference (cm)	89.5 ± 8.6	93.2 ± 11.3	86.3 ± 3.8	0.13
Hip Circumference (cm)	108.8 ± 8.6	110.1 ± 13.5	107.7 ± 7.8	0.67
Waist/hip ratio	0.81 ± 0.14	0.84 ± 0.04	0.79 ± 0.37	0.50
Fat mass (Kg)	23.1 ± 7.1	20.8 ± 9.1	25.1 ± 4.6	0.25
Percent body fat (%)	31.3 ± 6.6	26.3 ± 6.1	35.7 ± 4.6	0.002
Free fat mass (%)	50.2 ± 9.7	56.2 ± 10.9	44.9 ± 4.6	0.02

Table 3: Clinical and biochemical parameters before and after intensive insulin intervention.

	Before insulin intervention	After insulin intervention	p-value
Number of Subject (n)	15	15	
Systolic blood pressure (mmHg)	119.6 ± 12.6	122.3 ± 11.1	0.38
Diastolic blood pressure (mmHg)	74.1 ± 8.4	76.4 ± 6.7	0.13
Weight (Kg)	73.3 ± 14.1	75.2 ± 13.6	0.02
Body mass index (Kg/m^2)	26.4 ± 3.9	27.0 ± 3.5	0.03
Waist circumference (cm)	89.5 ± 8.6	91.0 ± 7.6	0.01
Hip Circumference (cm)	108.8 ± 8.6	108.8 ± 10.3	0.98
Waist/Hip ratio	0.81 ± 0.14	0.83 ± 0.05	0.008
Fat mass (Kg)	23.1 ± 7.1	28.2 ± 6.4	< 0.001
Percent body fat (%)	31.3 ± 6.6	21.2 ± 6.3	< 0.001
Free fat mass (%)	50.2 ± 9.7	54.0 ± 10.6	< 0.001
Insulin sensitivity (%/minute)	1.98 ± 0.23	2.26 ± 0.18	< 0.001
Fasting capillary glycemia (mg/dL)	385.4 ± 98.6	134.4 ± 18.2	< 0.001
Total cholesterol (g/L)	1.68 ± 0.25	1.52 ± 0.30	< 0.001
Triglyceride (g/L)	1.08 ± 0.55	1.05 ± 0.46	0.71
HDL cholesterol (g/L)	0.64 ± 0.33	0.68 ± 0.32	0.30
LDL cholesterol (g/L)	0.83 ± 0.36	0.62 ± 0.37	< 0.001
Urine glucose (mg/dL)	313.3 ± 310.2	00.00	0.002

subjects. No significant difference was observed for fat mass ($p = 0.25$), BMI ($p = 0.62$) or waist circumference ($p = 0.13$), but it was noted that these values were higher in male subjects than in female subjects. Table 2 presents the baseline clinical and anthropometric parameters.

Insulin sensitivity at baseline

The mean insulin sensitivity of all patients at baseline was 1.98 ± 0.23 %/minute. There was no significant difference (p value = 0.73) in the insulin sensitivity at baseline between the male (2.01 ± 0.19%/min) and the female subjects (1.96 ± 0.27%/min). All 15 patients had KITT values less than 2.5%/minute at baseline.

Effects of the intervention

The mean insulin dose at baseline was 82.0 ± 17.6 IU/day. Male subjects required slightly higher insulin doses, 84.0 ± 16.0 IU/day than female subjects, 80.2 ± 19.9 IU/day, ($p = 0.69$). There was a significant increase ($p < 0.001$) in the insulin sensitivity compared before (1.98 ± 0.23 %/min) and after (2.26 ± 0.18 %/min) the intensive insulin intervention. Fasting capillary glucose levels decreased from 384.4 ± 98.6 mg/dL before the intervention to 134.4 ± 18.2 after intervention ($p < 0.001$) (Table 3).

The results of our study showed that, there was an overall improvement in insulin sensitivity in all participants. Male participants were characterised by higher SBP and DBP values, BMI, greater weight, waist circumference, waist-to-hip ratio, higher free fat mass, and higher total cholesterol values whereas females had a higher mean percent body fat. The lipid profile showed less significant changes before and after the intervention; there was a significant decrease of the total cholesterol and LDL levels. There was a decrease in the triglyceride level and an increase in the HDL cholesterol level but which were not significant.

Discussion

The result of the SITT showed that all the participants initially were resistant to insulin given the cut-off of insulin resistance set at KITT < 2.5%/minute. This finding is contrary to Lee *et al.* in 2008, where 57% in a group of 83 type 2 diabetic patients were insulin resistant at baseline evaluation [15]. This difference can be accounted for by the fact that, the mean insulin sensitivity of their diabetic population is known and so it was easy to classify them into insulin sensitivity states. Their study lasted 25 months, much longer than 1 week. However, our primary outcome was not to classify patients according to their insulin sensitivity state but to investigate whether after 1 week of intensive insulin therapy, we can have an improvement in the insulin sensitivity.

The dose of insulin used for the intervention was quite high compared to similar studies. In 2008, Chen *et al.* [16] used an insulin dose of 26.4 ± 10.5 IU/day for their intervention. This could be explained by the fact that, we used a more precise method to directly estimate the insulin dose of our patients while their insulin dose was calculated by weight and it was a step-wise titration since the duration of their follow-up was 6 months as compared to 1 week in our study. Another possible explanation could be the reduced insulin sensitivity of our patients at baseline and also the participants were all severely hyperglycemic. Ryan *el al.* [11] had subjects who were still hyperglycemic after 2 weeks of intensive insulin therapy using a step-wise up-titration method also.

Concerning changes in the lipid profile; in 2008, Weng *et al.* [14] had a similar decrease in total cholesterol, triglyceride, free fatty acids and LDL-cholesterol after 3 weeks of intensive insulin therapy using the continuous subcutaneous insulin infusion (CSII). But only the decrease in LDL-cholesterol and free fatty acids were significant. In another study carried out using high dose insulin during a hyperinsulinemic euglycemic clamp [17], there was a significant decrement in total cholesterol, LDL cholesterol and triglyceride levels after 2 hours of intervention. This was probably due to the enhanced LDL oxidizability induced by insulin and the fact that insulin is capable of up regulating LDL receptors [17].

This is the first time a study is carried out to investigate the effects that a one week intensive insulin intervention has on insulin sensitivity in our local setting. The overall improvement seen in insulin sensitivity and blood glucose control goes further to explain the dose-response relationship and also importance of insulin in the design of therapeutic regimens in diabetic patients. The significant decrease in blood glucose level, LDL cholesterol, total cholesterol and the decrease trend seen in triglyceride levels were indicators of the reduction in glucotoxicity and lipotoxicity. However, some of the weaknesses of this study could be the absence of independent controls, the small sample size and the absence of free fatty acids (FFA) assays and the difficulty to regulate caloric intake. It was difficult to theoretically impute all of the observed finding to the intervention since a control group was not used. We however limited confounders through our method of selection and the procedure used in the study. Free fatty acid assay gives a direct measure of lipotoxicity since it is the direct product of the catabolism of lipids. Nonetheless,

the reduction in LDL cholesterol and total cholesterol give us a global picture of lipid homeostasis after the intervention. During the study, it was difficult to regulate the caloric intake since we did not prepare well standardized meals for our patients.

Conclusion

In clinical practice, improvement of insulin sensitivity of type 2 diabetic patients can curb the progression of the disease and can prevent the advent of the complications due to diabetes. The implications of these findings are enormous since it supports the initiation of an intensive insulin intervention in all patients having glucose toxicity/lipotoxicity and especially in regions where "clinical inertia" (defined as the lack of initiation, or intensification of therapy when clinically indicated) and misconception about insulin therapy predominate.

Acknowledgements

We acknowledge the nursing staff of the National Obesity Centre and the Diabetes and Metabolic Disease Unit of the Yaoundé Central Hospital. We also wish to acknowledge all the patients who participated in this study. Parts of this article has been presented as an abstract at the French-speaking Annual Diabetes Congress, Montpellier, France, 26th-29th March 2013.

References

1. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15: 539-553.
2. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, et al. (1991) A two-step model for development of non-insulin-dependent diabetes. Am J Med 90: 229-235.
3. Nathan DM (2002) Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. N Engl J Med 347: 1342-1349.
4. Poitout V, Robertson RP (2002) Minireview: Secondary beta-cell failure in type 2 diabetes--a convergence of glucotoxicity and lipotoxicity. Endocrinology 143: 339-342.
5. Sivitz WI (2001) Lipotoxicity and glucotoxicity in type 2 diabetes. Effects on development and progression. Postgrad Med 109: 55-59, 63-64.
6. Haopeng Yang, Xuejun Li (2012) The role of fatty acid metabolism and lipocthropy in pancreatic B-cell injury: Identification of potential therapeutc targets. Diabetes and Obesity 4: 396-402.
7. Della Casa L, del Rio G, Glaser B, Cerasi E (1991) Effect of 6-month glicazide treatment on insulin release and sensitivity to endogenous insulin in NIDDM: role of initial continuous subcutaneous insulin infusion-induced normoglycemia. Am J Med 90: 37S-45S.
8. Rossetti L (1995) Glucose toxicity: the implications of hyperglycemia in the pathophysiology of diabetes mellitus. Clin Invest Med 18: 255-260.
9. Glaser B, Cerasi E (1999) Early intensive insulin treatment for induction of long-term glycaemic control in type 2 diabetes. Diabetes Obes Metab 1: 67-74.
10. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG (1985) The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 34: 222-234.
11. Ryan EA, Imes S, Wallace C (2004) Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care 27: 1028-1032.
12. Kengne AP, Djouogo CF, Dehayem MY, Fezeu L, Sobngwi E, et al. (2009) Admission trends over 8 years for diabetic foot ulceration in a specialized diabetes unit in cameroon. Int J Low Extrem Wounds 8: 180-186.
13. Park J-S, Kim C-S, Nam J-Y, Kim D-M, Jo M-H, et al. (2005) Characteristics of Type 2 Diabetes in Terms of Insulin Resistance in Korea. Yonsei Med J 46: 484-490.
14. Weng J, Li Y, Xu W, Shi L, Zhang Q, et al. (2008) Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 371: 1753-1760.
15. Lee MY, Koh JH, Nam SM, Jung PM, Sung JK, et al. (2008) Short insulin tolerance test can determine the effects of thiazolidinediones treatment in type 2 diabetes. Yonsei Med J 49: 901-908.
16. Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, et al. (2008) Beneficial effects of insulin on glycemic control and beta-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. Diabetes Care 31: 1927-1932.
17. Quinones-Galvan A, Sironi AM, Baldi S, Galetta F, Garbin U, et al. (1999) Evidence That Acute Insulin Administration Enhances LDL Cholesterol Susceptibility to Oxidation in Healthy Humans. Arterioscler Thromb Vasc Biol 19: 2928-2932.