Severe hypertriglyceridaemia in Type 2 diabetes mellitus: beneficial effect of continuous insulin infusion

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Summary

Background: Severe hypertriglyceridaemia is a recognized complication of Type 2 diabetes mellitus (T2DM); however, there is no consensus on acute management despite the significant risk of developing associated complications such as acute pancreatitis and hyperviscosity syndrome.

Aim: To identify the association between hyperglycaemia and severe hypertriglyceridaemia in patients with T2DM and assess the effect of continuous insulin infusion therapy on serum triglyceride (TG) concentrations and report any adverse events associated with this therapeutic approach.

Design: Retrospective review of case records.

Methods: Patients with uncontrolled hyperglycaemia and severe hypertriglyceridaemia (serum TG > 15 mmol/l) treated with continuous intravenous insulin infusion between October 2008 and September 2009 were retrospectively evaluated (n = 15). Details recorded included demographics, admission details, lipid profiles, glycaemic control, serum amylase and adverse events. Patients receiving treatment-dose unfractionated heparin infusion were excluded.

Results: Severe hypertriglyceridaemia is associated with hyperglycaemia in our heterogeneous group of patients with T2DM presenting with new-onset diabetes or established disease on pre-existing insulin or oral hypoglycaemic agents. Administration of continuous exogenous insulin not only achieved normoglycaemia but also dramatically corrected severe hypertriglyceridaemia in all patients (P = 0.001).

Conclusions: The administration of continuous insulin in patients with T2DM with severe hypertriglyceridaemia is a simple and safe method of significantly reducing the immediate risk associated with this metabolic complication and should be considered in any T2DM patient presenting with severe hypertriglyceridaemia and hyperglycaemia.

Introduction

Patients with Type 2 diabetes mellitus (T2DM) are susceptible to the detrimental effects of insulin resistance affecting hepatic, muscle and adipose tissue and frequently present with the classic triad of hyperinsulinaemia, hyperglycaemia and hypertriglyceridaemia. Severe hypertriglyceridaemia is a recognized feature of T2DM and requires aggressive management in order to minimize the development of associated complications such as acute pancreatitis and hyperviscosity syndrome. The incidence of acute pancreatitis as a result of hypertriglyceridaemia is considered to account for ~10% of all acute pancreatitis cases with a further 56% frequency in gestational acute pancreatitis.1,2 In addition, atherosclerosis is far more common in T2DM and although is appreciated to have a multifactorial aetiology, hypertriglyceridaemia has been reported as an independent risk factor for coronary vascular disease even after adjustment for high-density lipoprotein cholesterol.3
Triglyceride (TG)-rich lipoproteins include pre-β lipoproteins (very low-density lipoprotein, VLDL) and chylomicron particles. Hypertriglyceridaemia is essentially a result of excessive hepatic endogenous synthesis of VLDL particles. The mechanism behind such increased TGs production is not fully understood in T2DM and has largely been attributed to reduced adipose tissue lipoprotein lipase activity, an enzyme critical to the clearance of serum TG. However, hepatic insulin resistance and resultant relative circulating insulin deficiency are known to lead to considerable lipogenesis with overproduction of VLDL as well as increase in free fatty acids and cholesteryl ester transfer protein activity.

Management of hypertriglyceridaemia in diabetes remains controversial and consists of non-pharmacological and pharmacological treatment according to serum TG levels. The clinical presentation of severe hypertriglyceridaemia ranges from asymptomatic biochemical detection to eruptive xanthoma, hepatosplenomegaly, abdominal pain and acute pancreatitis, lipaemia retinalis, peripheral neuropathy and neurological deficit. Rapid resolution of lipid abnormalities greatly influences patient outcome and it is recognized that severe hypertriglyceridaemia should be treated promptly in order to reduce associated complications. However, approach to immediate management of severe hypertriglyceridaemia in patients with T2DM remains varied. Effective lowering of serum TG has been observed following the use of 5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, omega-3-acid ethyl esters, fibrates and niacin. In addition, several case reports and case series have demonstrated improvement in serum TG levels following administration of continuous insulin infusion. Although such reports show a beneficial effect on hypertriglyceridaemia and hyperglycaemia, a maximal number of four patients with T2DM have been studied and confounding factors exist, such as the additive effect of unfractionated heparin on peripheral lipoprotein lipase activity.

In comparison, we highlight treatment of 15 patients presenting with hyperglycaemia and severe hypertriglyceridaemia associated with T2DM and show the rapid and safe correction of hypertriglyceridaemia following continuous insulin infusion in the absence of apheresis, unfractionated heparin or other reported treatment strategies.

**Patients and methods**

Patients admitted over a 12-month period from October 2008 with hyperglycaemia and severe hypertriglyceridaemia (serum TG > 15 mmol/l) were retrospectively reviewed. Details recorded included demographics, reason for admission and previous diabetes and lipid treatment. Serial lipid profiles were outlined alongside daily blood glucose measurements, glycated haemoglobin (HbA1c), and thyroid function and serum amylase. Testing for the presence of anti-glutamic acid decarboxylase and anti-insulin-specific antibodies was reviewed as well as screening for genetic mutations to help exclude Type 1 DM and monogenic DM.

Continuous intravenous insulin infusion was administered in all cases. Additional lipid-lowering therapy varied according to clinical indication and included HMG Co-A reductase inhibitors, omega-3-acid ethyl esters (Omacor) and fibrates. Prophylactic low-molecular weight heparin was given to all patients (Enoxaparin 20–40 mg). However, patients receiving continuous unfractionated heparin infusion were excluded due to the possible confounding activating effect upon lipoprotein lipase function. Patient outcome, length of hospital stay and adverse events were identified.

Descriptive statistics were calculated using Microsoft Excel™ and Wilcoxon sign rank tests performed with GraphPrism™ software. For non-Gaussian distributed data, non-parametric statistics were used.

**Results**

A total of 15 patients received continuous intravenous insulin infusion for the treatment of severe hypertriglyceridaemia associated with hyperglycaemia. Mean patient age was 46 (27–70) years. Ethnic groups included eight Caucasian, five Afro-Caribbean and two Indo-Asian patients. The average insulin infusion duration was 48 h (24–72) and varied according to disease severity. Median total insulin units infused measured 72 U (48–136) following 24 h, 57 U (46–102) at 48 h and 33 U (24–64) after 72 h insulin administration. DM was previously diagnosed in eight patients with mean disease duration measuring 60 (2–96) months, thus leaving seven patients who presented with newly diagnosed DM. Median admission body mass index measured 32.6 (25.3–47.6) kg/m².

Three of the patients presented with acute pancreatitis most likely induced by severe hypertriglyceridaemia. First-degree family history of T2DM was recorded in six (n = 15) patients. Diabetic ketoacidosis was not identified in any patient. Interestingly, new-onset T2DM was identified in seven patients presenting with hyperglycaemia and severe hypertriglyceridaemia and four patients were already on atypical antipsychotics, such as olanzapine, which are known to be associated with hyperglycaemia.
and hypertriglyceridaemia. There was no biochemical evidence of thyroid dysfunction or nephrotic syndrome in this cohort which is a relevant observation given that hypothyroidism and severe proteinuria can be associated with hyperlipidaemia. Previous lipid-lowering treatment prior to admission was utilized in seven patients and included combination and single agent therapy; statins (n=5), fenofibrate (n=2), omega-3-acid ethyl esters (Omacor®) (n=3) and Ezetimibe (n=1).

Table 1 outlines patient clinical characteristics. Median HbA1c on admission measured 9.6% (81 mmol/mol) (6.1–16.1%/43–152 mmol/mol). Pre-admission insulin therapy was utilized in 75% (n=6) and Metformin in 25% (n=2) patients. Figure 1 outlines trend in serum TGs. Median admission serum TG measured 26.23 mmol/l (15.09–48.43) and serum cholesterol 11.24 mmol/l (5.39–19.62). Median serum TG reduced to 15.79 mmol/l (0.79–36.59) following only 24 h insulin infusion (n=15) and 12.15 mmol/l (5.74–32.49) after 48 h duration (n=8). Insulin infusion continued for 72 h in seven patients with median serum TG measuring 10.20 mmol/l (5.74–24.03). Subcutaneous insulin was continued on discharge in 80% (n=12) of patients with oral hypoglycaemic agents used in the remaining group. Median discharge serum TG measured 5.75 mmol/l (0.79–11.66) and serum cholesterol 5.90 mmol/l (3.65–10.74) correlating with significant reduction in serum TGs following treatment with intravenous insulin (P=0.001).

Concomitant lipid-lowering therapy included statins (n=9) and omega-3-acid ethyl esters (n=9). Continued administration of Fenofibrate occurred in two patients. Prophylactic low-molecular weight heparin was given to all patients (Enoxaparin 20–40 mg) as outlined. Median length of hospitalization was 4 (3–15) days with hospital mortality occurring in one patient in association with severe acute pancreatitis. There were no immediate complications or adverse events documented following the administration of continuous insulin infusion, statins, Omacor® or fibrates. Autoantibody testing was performed in five patients based on clinical suspicion with no positive anti-glutamic acid decarboxylase or islet cell antibodies detected.

Glycaemic control was achieved by continuous insulin infusion in all patients in the first 24 h. Median serum glucose measured 20.6 mmol/l (14.7–38.7) at 24 h, 17 mmol/l (11.4–19.9) at 48 h and 10 mmol/l (9.3–18.2) at 72 h. Trends in serum glucose concentration, including maximal and minimal values over each 24-h period, are outlined in Figure 2.

**Discussion**

These results detail severe hypertriglyceridaemia (>15 mmol/l) associated with hyperglycaemia in a heterogeneous group of patients with T2DM ranging from new-onset T2DM to established disease on pre-existing insulin or oral hypoglycaemic agents. Continuous insulin infusion was administered rather than intermittent subcutaneous insulin injection in order to control hyperglycaemia at initial presentation and allow appropriate estimation of further insulin requirements. It is noteworthy that a majority of the patients were obese and presented with poor glycaemic control. In addition, four were taking atypical anti-psychotic drugs which may result in weight gain, hyperglycaemia and hypertriglyceridaemia. Quick and efficient

![Figure 1. Median admission serum TG measured 26.23 mmol/l (15.09–48.43). Median discharge serum TG measured 5.75 mmol/l (0.79–11.66) and serum cholesterol 5.90 mmol/l (3.65–10.74) correlating with significant reduction in serum triglycerides following intravenous insulin (P=0.001).](image-url)
treatment of severe hypertriglyceridaemia is vital to reducing the risk of associated acute pancreatitis, and of course it should be remembered that the diagnosis of acute pancreatitis can be difficult in this setting, as amylase assay in severely lipaemic serum samples can give spuriously low results and in such cases urine amylase determination may be helpful.12

The combined use of insulin and unfractionated heparin in the treatment of severe hypertriglyceridaemia has been reported in a few case series and has been shown to be successful even in the absence of DM.9,10 Endothelial lipoprotein lipase release is increased in the presence of unfractionated heparin,11 while exogenous insulin has a long-established effect on increasing peripheral synthesis of lipoprotein lipase contained in muscle and adipose tissue.12 In this report, administration of continuous insulin infusion achieved not only necessary glycaemic control in T2DM patients but also dramatically corrected severe hypertriglyceridaemia in all patients. Additional lipid-lowering therapy was initiated in almost half of cases and optimized in the remaining group. Importantly, patients receiving therapeutic unfractionated heparin anticoagulation and those with previously known inherited dyslipidaemic states were excluded. Therefore, the sole administration of continuous insulin infusion appears to have been the consistent intervention across the cohort, which importantly correlated with significant reduction in serum TG.

There are some clues as to how insulin therapy can reduce severe hypertriglyceridaemia beyond increasing peripheral lipoprotein lipase activity. Hyperglycaemia is associated with resistance of hepatic transcription factor FoxO1 and adipose tissue lipoprotein lipase to the actions of circulating endogenous insulin, resulting in uncontrolled gluconeogenesis and reduced hydrolysis of serum TG.13 However, following the development of liver-specific insulin receptor knockout mouse model, it has become apparent that total hepatic insulin resistance does not account for uncontrolled lipogenesis but rather selective insulin resistance better explains this metabolic disturbance.16

Recent research supports this finding following recognition that hepatic TG production remains sensitive to circulating insulin, through the activation of transcription factor SREBP-1c. Elevated nuclear SREBP-1c promotes fatty acid synthesis, hepatic TG production and serum VLDL secretion.17

To date, reports of the effect of insulin therapy alone in the treatment of severe hypertriglyceridaemia are limited to case reports8,18,19 and a case series consisting of only seven patients.20 Tamer-Perez et al.20 demonstrated a reduction in TG concentration from >1000 mg/dl (≈11.29 mmol/l) to <400 mg/dl (≈4.52 mmol/l) following 60 h of continuous insulin infusion. However, only four patients had T2DM, two of which also had anti-retroviral medication co-administered, and the remaining three patients presented with severe acute pancreatitis.20 In comparison, we report the safe and effective treatment of hyperglycaemia and severe hypertriglyceridaemia following continuous insulin infusion in 15 patients with T2DM and show a significant reduction, respectively, with this simple and cost-effective method.

In conclusion, the administration of continuous intravenous insulin infusion in this cohort was safe and extremely successful in rapidly correcting severe hypertriglyceridaemia while maintaining glycaemic control. Severe hypertriglyceridaemia poses significant risk to patients with T2DM and prompt effective management is vital in reducing associated morbidity and mortality. There is no consensus on the immediate treatment of severe hypertriglyceridaemia and these observations offer valuable insight into providing simple strategies to patients which may reduce immediate risk. Continuous infusion of insulin appears to be beneficial in restoring serum hypertriglyceridaemia and normoglycaemia. Ultimately, continuous insulin infusion is a relatively common treatment modality offered to patients with T2DM and yet may offer far more than simply glycaemic control but rather restore hepatic selective insulin resistance; a biochemical disturbance at the crux of metabolic disorder.

Conflict of interest: None declared.

References
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