

# Reduction in Serum Triglyceride Levels in Diabetic Patients May Result in Decreased Insulin Dependence and Disease Regression

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**ABSTRACT:** **Background:** Type 2 diabetes mellitus is a multifactorial disease in which genetic susceptibility and environmental factors induce pancreatic  $\beta$ -cell dysfunction and insulin resistance. Additional factors such as hyperglycemia and hyperlipidemia have roles in  $\beta$ -cell dysfunction and disease progression. The phenomenon of lipid-induced pancreatic  $\beta$ -dysfunction, designated as lipotoxicity, has been observed in several in vitro and in vivo experiments; however, there is still no solid evidence for the occurrence of this event in humans. The toxic effect of high lipid levels on  $\beta$ -cell function consists of impaired insulin gene expression, apoptosis, and reduced glucose-stimulated insulin secretion.

**Objectives:** To demonstrate the importance of treating hypertriglyceridemia in reducing glucose intolerance and the need for insulin therapy in hospitalized diabetic patients.

**Methods:** We evaluated five clinical case reports and conducted a detailed literature review via the PubMed search engine.

**Results:** Reduction in elevated blood triglyceride and glucose levels in hospitalized diabetic patients resulted in a rapid decline in glucose levels and in the need for insulin therapy.

**Conclusions:** A decrease in high triglyceride levels in “lipotoxic” diabetic patients may improve insulin intolerance and glucose homeostasis and reduce the need for insulin therapy.

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**KEY WORDS:** diabetes mellitus, glucotoxicity, insulin dependence, insulin therapy, lipotoxicity

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**D**iabetes mellitus is defined as a syndrome of impaired glucose homeostasis characterized by disturbances in insulin secretion and resistance [1]. The multiple disorders in insulin homeostasis have led to the recognition that diabetes is polygenic in nature and may present by different phenotypes rather than as a single disease with one specific etiology and pathogenesis [1].  $\beta$ -cell dysfunction is known to play a major role in disease development and may be the common link in various pathologic processes in diabetic patients. Epidemiologic observations have revealed a correlation between obesity and

diabetes [2]. Notably, obesity is closely associated with hyperlipidemia, which is typically accompanied by a high plasma level of free fatty acids (FFA) [3]. This fact has prompted researches to investigate whether an elevated FFA level may damage  $\beta$  cells and whether this effect is dependent on high glucose levels. Several in vitro studies, as well as human experiments, have demonstrated negative effects of elevated levels of lipids and glucose on  $\beta$ -cell function in healthy and diabetic individuals. This phenomenon is known as lipotoxicity and glucotoxicity [4]. Moreover, targeting lipid levels in diabetic patients has been shown to reduce cardiovascular morbidity and to improve outcomes for diabetic individuals as a group [5]. Yet, clinical evidence is sparse regarding the role of lipotoxicity in the development and management of type 2 diabetes. We describe five patients with high blood glucose levels and hypertriglyceridemia, for whom targeting serum triglyceride levels led to a decline in insulin dose requirements.

## PATIENTS AND METHODS

### CASE SERIES

#### Case 1

Z.D., a 46 year old male who worked as an accountant, was admitted to the hospital because of excessive thirst and polyuria, poor appetite, and a weight loss of 7 kg during the preceding 2 months. His medical history was unremarkable. Both of his parents were known to have impaired glucose tolerance (IGT). Physical examination showed body mass index (BMI) 28.4 kg/m<sup>2</sup>, body temperature 36°C, a moist oral cavity, blood pressure 182/115 mmHg, and a pulse rate of 98 beats per minute. On physical examination, there were no abnormalities of the heart, lungs, or abdomen. Laboratory findings at admission revealed triglycerides 1381 mg/dl, total cholesterol 284 mg/dl, and serum amylase levels within normal range [Table 1]. Fasting blood glucose level was 244 mg/dl, arterial pH was within normal range, urine analysis was positive for ketone bodies and HbA1c was 12.3% (National Glycohemoglobin Standardization Program). Tests for anti-glutamic acid decarboxylase (GAD) and anti-islet cells were negative. Following the diagnosis of diabetes, a basal bolus insulin injection regimen was started

with 12 units/day before meals of glulisine (Apidra-Sanofi, S.A, Gentilly, France) and 8 unit/day before bedtime of glargine (Lantus-Sanofi, S.A., Gentilly, France). These medications were accompanied with intravenous administration of normal saline (1 L/day), omega 3 (1 g/day), and 400 mg/day of bezafibrate (Boehringer Mannheim, Rotkreuz, Switzerland). Under this regimen, the serum glucose and triglycerides decreased to 230 mg/dl and 220 mg/dl, respectively. The patient was discharged on 0.6 mg per day liraglutide (Victoza, Novo Nordisk, Bagsværd, Denmark), 10 units/day glargine, 400 mg/day bezafibrate, and 850 grams twice a day metformin. After 2 months, blood analysis revealed a triglycerides serum level of 145 mg/dl, total cholesterol 197 mg/dl, and glucose values within normal range, with HbA1c of 5.9% without applying insulin injections.

#### Case 2

Y.L., a 42 year old male, was referred to our department because of uncontrolled serum glucose and triglyceride levels. His medical history was remarkable for morbid obesity with BMI of 30 kg/m<sup>2</sup>, diabetes mellitus type 2, hypertension, and hyperlipidemia. His medications comprised 36 units/day insulin aspart, 50 units/day insulin detemir, and 100 mg/day ciprofibrate. On admission, his blood pressure and pulse rate were 131/89 mmHg and 77 beats per minute, respectively. A physical examination was unremarkable. Laboratory findings revealed triglycerides 860 mg/dl, total cholesterol 227 mg/dl, fasting blood glucose of 298 mg/dl, arterial pH within normal range, absence of urinary ketone bodies, and HbA1c 12.8% [Table 1]. The patient was given insulin basal bolus injections of 18 units/day glulisine and 32 units/day glargine, in addition to 100 mg/day ciprofibrate, and intravenous administration of normal saline (1 L/day). Following this treatment, the serum glucose and triglyceride levels declined to 220 mg/dl and 426 mg/dl, respectively. Total cholesterol was 173 mg/dl. The patient was discharged with basal bolus insulin of 46 units/day, 100 mg/day ciprofibrate, and 1 g/day omega 3. At the next follow-up, fasting glucose was 330 mg/dl, HbA1c 11%, triglycerides 1321 mg/dl, and total cholesterol 212 mg/dl. The patient remained fully dependent on insulin and was prescribed continued treatment with 18 units/day glulisine, 32 units/day glargine, and 100 mg/day ciprofibrate.

#### Case 3

S.L., a 54 year old male, was admitted to the hospital because of polydipsia and polyuria of 2 weeks duration. His medical history was unremarkable and he was not taking any medicines. His BMI was 30.8 kg/m<sup>2</sup>. Physical examination was unremarkable, body temperature 36.5°C, pulse rate 80 beats per minute, and blood pressure 136/82 mm/Hg. His mucosal membranes were dry. The triglyceride level was 5116 mg/dl, total cholesterol 690 mg/dl, fasting blood glucose level 280 mg/dl, and HbA1c 13.8% [Table 1]. Arterial pH was within normal range, no ketone bodies were found in the urine, and blood amylase levels were normal. The values of C peptide, anti-islet cell, and anti-GAD were normal. Diabetes mellitus was diagnosed and the patient was placed on a regimen of basal-bolus insulin injections with 6 units/day glulisine, 6 units/day glargine, 400 mg/day bezafibrate, and intravenous normal saline infusion (1 L/day). Under this regimen, fasting glucose level was reduced to 128 mg/dl, triglycerides 726 mg/dl, and total cholesterol 493 md/dl. On discharge, the patient was advised to continue treatment with 6 units/day of glargine, 850 mg metformin twice a day, and 400 mg/day bezafibrate. At 6 months follow-up, the patient was taking 850 mg metformin twice a day and 400 mg/day bezafibrate without insulin. Blood tests revealed fasting glucose 80 mg/dl, triglycerides 200 mg/dl, total cholesterol 180 mg/dl, and HbA1c 6.2%.

#### Case 4

S.Y., a 38 year old musician, was admitted because of polydipsia polyuria and weight loss during the preceding 6 months. His medical history was unremarkable, his family history was positive for diabetes mellitus. Physical examination was without pathological findings. The patient's BMI was 30.4 kg/m<sup>2</sup>, his oral cavity was moist, blood pressure was 185/114 mmHg, and pulse rate was 85 beats per minute. Laboratory findings revealed a triglyceride level of 2000 mg/dl, total cholesterol 340 mg/dl, and serum amylase within the normal range. Fasting glucose was 243 mg/dl, arterial pH was within normal range, no ketone bodies were found in the urine, and HbA1c was 13% [Table 1]. Tests for anti-GAD and anti-islet cell were negative. A basal bolus regimen of 10 units/day glargine and 30 units/day glulisine was started, together with 400 mg bezafibrate per day. Following this regimen, plasma glucose level and triglycerides decreased to 120 mg/dl and 300 mg/dl, respectively, and total cholesterol to 285 mg/dl. The patient was discharged on 10 units/day glulisine, 400 mg bezafibrate per day, and 850 grams metformin twice a day. One month later, insulin was replaced by metformin 850 mg twice a day. After 2 months, blood analysis showed serum triglyceride levels were stable at 124 mg/dl, total cholesterol 206 mg/dl, and fasting glucose 109 mg/dl.

#### Case 5

A.T., a 27 year old male, was admitted because of polydipsia, polyuria, and blurred vision of 5 days duration. His medical

**Table 1.** Patient characteristics

Patient	Age	Medical history	Gender	BMI	Family history	TRG mg/dl	FPG mg/dl	TC mg/dl	HbA1c
Z.D.	46		Male	28.4	positive	1381	244	284	12.3%
Y.L.	42	Diabetes, hypertension and hyperlipidemia	Male	30.0	negative	860	298	227	12.8%
S.L.	52		Male	30.8	negative	5116	280	690	13.8%
S.Y.	38		Male	30.4	positive	2000	450	340	13.0%
A.T.	27	Hyperlipidemia	Male	30.0	positive	1374	432	283	6.6%

BMI = body mass index, FPG = fasting plasma glucose, TC = total cholesterol, TRG = triglycerides

history was remarkable for hyperlipidemia, his family history was positive for diabetes mellitus. On physical examination, there were no abnormalities. Eye examination was unremarkable. The patient's BMI was 28.4 kg/m<sup>2</sup>, oral cavity was moist, and blood pressure and pulse rate were 150/104 mmHg and 99 beats per minute, respectively. Laboratory findings revealed triglycerides 1347 mg/dl and total cholesterol 283 mg/dl. Fasting blood glucose was 432 mg/dl, arterial pH was within normal range, no ketone bodies were found in the urine, and HbA1c was 6.8% [Table 1]. Tests for anti-GAD and anti-islet cell were all negative. A regimen of basal bolus insulin injections was started with 8 units/day glulisine and 6 units/day glargine, together with 1 g/day omega 3, and 400 mg/day bezafibrate. Under this regimen, the fasting blood glucose level and triglycerides decreased to 807 mg/dl and 107 mg/dl, respectively. On his last day of hospitalization, blood glucose levels were in the normal range and the patient was treated with only 850 mg/day metformin, without insulin injections. He was discharged with 850 mg/day metformin and 400 mg/day bezafibrate. At 2 months follow-up, blood analysis revealed triglycerides 372 mg/dl, total cholesterol 225 mg/dl, and fasting glucose levels 80 mg/dl, with HbA1c of 5.5% without insulin treatment.

All patients had dietetic counseling during hospitalization and were advised to consume a diet low in simple carbohydrate.

**RESULTS**

All five patients had high blood levels of triglycerides, glucose, and HbA1c. In addition, all were obese and diagnosed with

diabetes [Table 1]. Assuming that all five endured lipotoxicity, we decided that targeting the high triglyceride levels, along with hyperglycemia, could contribute to restoring glucose hemostasis on one hand and to reducing patient dependence on insulin on the other. Following this approach, we noticed the appearance of an inverse relationship between triglyceride levels and the amount of insulin required to maintain glucose homeostasis [Figure 1]. During successive follow-up visits, we observed that four of our patients, along with normalization of triglyceride levels, attained normal levels of blood plasma glucose and HbA1c without requiring insulin injections at all [Figure 1A, Figure 1C, Figure 1D, Figure 1E]. In one patient, however, elevated triglyceride levels persisted, probably due to low adherence to treatment. He still needed high doses of insulin to maintain glucose levels in the normal range [Figure 1B].

It seems plausible that reducing levels of triglycerides in lipotoxic patients can attenuate the toxic effect on pancreatic β cells and contribute to decreased dependency on insulin therapy, and even to the level of restoring normal glucose hemostasis.

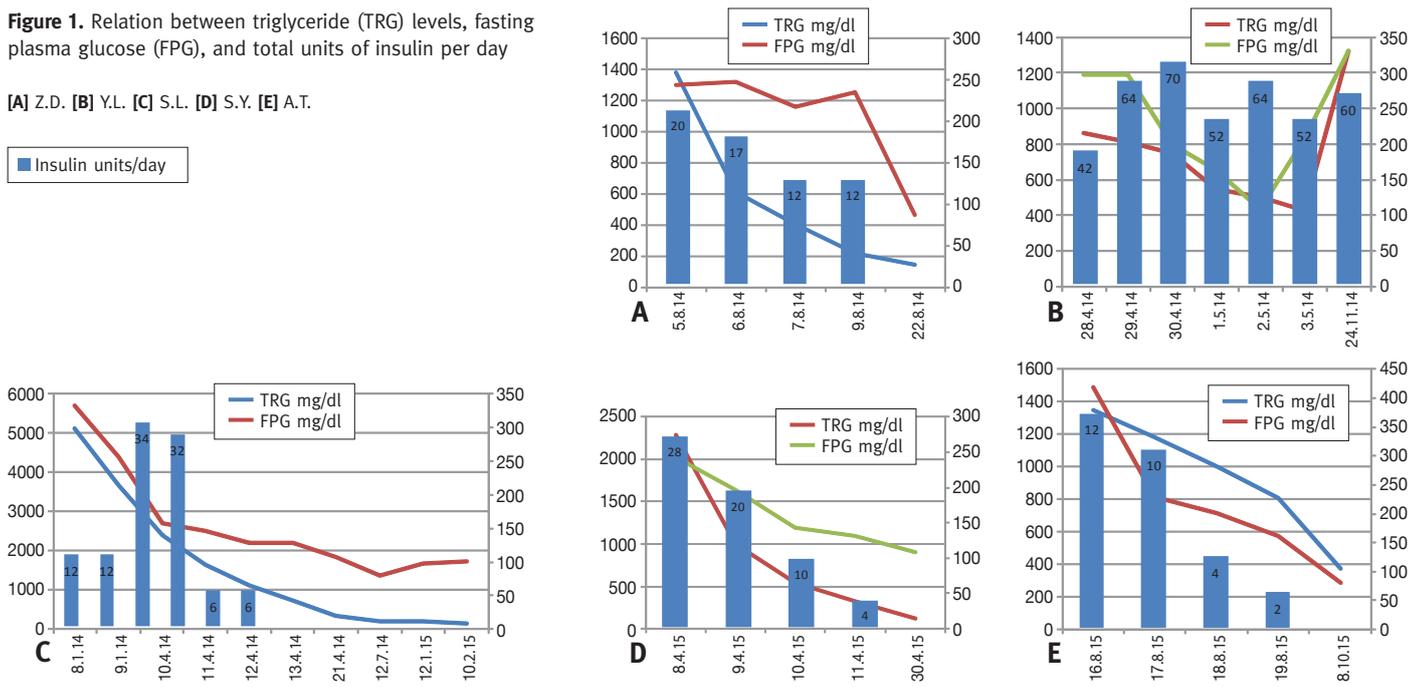
**DISCUSSION**

Type 2 diabetes mellitus is a heterogeneous syndrome of polygenic origin that involves both defective insulin secretion and peripheral insulin resistance [6]. High lipid and glucose values have been known to play important roles in pancreatic β-cell dysfunction, and thus to contribute to the pathogenesis of diabetes and disease progression. The toxic effect of lipids on β cells was first demonstrated by Unger et al. [4,7]. In a study

**Figure 1.** Relation between triglyceride (TRG) levels, fasting plasma glucose (FPG), and total units of insulin per day

[A] Z.D. [B] Y.L. [C] S.L. [D] S.Y. [E] A.T.

■ Insulin units/day



conducted on Zucker rats, they showed that FFA can induce functional impairment of  $\beta$ -cell glucose-stimulated insulin secretion (GSIS). In addition, they demonstrated that hyperglycemia can attenuate the secretory response of pancreatic  $\beta$  cells to glucose, and impair insulin-mediated glucose transport in different tissues, a phenomenon known as insulin resistance. These findings led to the terms glucotoxicity and lipotoxicity [4,8]. At a molecular level, a high level of fatty acids is believed to induce  $\beta$ -cell dysfunction by impairing gene expression of the insulin molecule and triggering cell apoptosis [9].

FFA are not always toxic, and at normal conditions they are essential for normal  $\beta$ -cell function. Acute exposure of  $\beta$  cells to fatty acids is known to increase GSIS [8,10]. However, prolonged exposure to FFA for more than 48 hours has been shown to inhibit  $\beta$ -cell GSIS. This phenomenon was observed in rats and later in humans [10]. Similarly, in a study carried out by Carpentier and colleagues [8], the increased insulin secretion observed in response to a rapid (90 minutes) lipid infusion in healthy subjects disappeared when the infusion was prolonged to 48 hours. This result reinforces the assumption that only long-lasting high levels of FFA are toxic to  $\beta$  cells and capable of reducing insulin secretion. While the negative effect of FFA on  $\beta$ -cell function has been well demonstrated in *in vitro* studies, efforts to reveal this effect in rats [10] and later in humans yielded inconsistent findings [8,11]. In this regard, according to a recent study [12] that compared apolipoprotein C3 (ApoC3)-transgenic mice (genetic predisposition to hypertriglyceridemia) to wild type littermates (without hypertriglyceridemia), blood glucose levels did not differ in response to glucose challenge or insulin tolerance tests. In addition, no differences were found in  $\beta$ -cell expression of insulin genes or in fat infiltration in the presence of high triglyceride levels. Nevertheless, recent studies demonstrated the deleterious effect of hypertriglyceridemia on  $\beta$ -cell function and insulin resistance. Mice who were hypertriglyceridemic due to heterozygotic knockout of the lipoprotein lipase gene, developed insulin resistance and IGT [13]. One cross sectional study that compared healthy men aged 20–65 years with high triglyceride levels (> 150 mg/dl) to normotriglyceridemic patients, reported that a significant association between fasting hypertriglyceridaemia and increased insulin secretion was an indication of abnormal  $\beta$ -cell function in a state of chronic exposure to elevated fasting triglycerides [14]. Recently, Feng et al. [15] demonstrated, in hypertriglyceridemic IGT patients, a significantly higher degree of insulin secretion but also a higher degree of insulin resistance and significantly reduced insulin sensitivity. In a study by Xiao et al. [16], an elevated triglyceride level, elevated BMI, and low level of high-density lipoprotein cholesterol were found to be independently associated with increased insulin resistance.

The inconsistency among studies may be explained in part by the means that insulin secretion is quantified *in vivo*. Elevated levels of FFA induce insulin resistance and promote a

rise in insulin demand and compensatory insulin hypersecretion (higher GSIS). In these circumstances, even if elevated, GSIS is confronted with increasing demand, and thus does not serve as a reliable indicator of  $\beta$ -cell function. Studies that accounted for this relationship were all conclusive that  $\beta$ -cell capacity to secrete insulin in the setting of rising insulin resistance is reduced after lipid infusion [15].

The relationship between lipotoxicity and diabetes was demonstrated in a study carried out by various teams of researchers [5,17]. Lipid infusion for a duration of 48 hours induced defective GSIS in type 2 diabetic patients only, whereas GSIS remained normal in healthy individuals. An association between lipotoxicity and positive family history of diabetes (FH+) has also been observed. Cusi [18] showed that acute intralipid infusion enhanced insulin secretion in a control group, as expected, but inhibited glucose-induced insulin secretion in FH+ individuals. This effect can be explained by the higher grade of  $\beta$ -cell exposure to FFA among FH+ individuals, due to enhanced spillover of fatty acids [17]. Fainaru and Schafer [19] also demonstrated the importance of metabolic background and energy consumption on plasma lipids and lipoproteins during fasting. Hence, it is reasonable to presume that initial damage to  $\beta$ -cell function promotes lipotoxicity; or, in other words, lipotoxicity may act as a second phenomenon that contributes to the progressive deterioration of already genetically damaged  $\beta$  cells. Another important aspect of  $\beta$ -cell lipotoxicity is related to the association between a lipid toxic effect and serum glucose levels. Hyperglycemia by itself can reduce the secretory response of pancreatic  $\beta$  cells to increments in glucose levels [7]. As for the relationship between lipotoxicity and glucotoxicity, Poitout and Robertson [20] demonstrated that prolonged *in vitro* exposure of isolated islets of diabetic Zucker rats to fatty acids decreases insulin gene expression in the presence of high glucose concentrations. Additional research has suggested that chronic hyperlipidemia is deleterious only in the context of concomitant hyperglycemia [21]. This finding led to the introduction of the term glucolipotoxicity. Although glucolipotoxicity has been demonstrated in both *in vitro* experiments and in rats [22], few studies have been conducted in humans, mainly because prolonged glucose infusions might be complicated with side effects.

Based on the above studies, glucolipotoxicity may be explained by the role of glucose in the partitioning of fatty acids in  $\beta$  cells [23]. In the presence of normal glucose levels, fatty acids are transported into the mitochondria, where they are processed via  $\beta$ -cell oxidation; whereas, higher glucose levels shift the intercellular fatty acid metabolism to cellular lipid synthesis, leading to cytosolic accumulation of lipid-derived signaling molecules and  $\beta$ -cell dysfunction [24].

## CONCLUSIONS

The case reports presented here as well as the literature review indicate that treating lipotoxicity by reducing triglyceride lev-

els in diabetic patients can result in rapid reduction in insulin dosages that were required to maintain normal blood plasma glucose levels. The impact of treating lipotoxicity on the progression, management, and prognosis of diabetes should be further investigated.

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**Capsule**

**Differential glucose requirement in skin homeostasis and injury identifies a therapeutic target for psoriasis**

Proliferating cells, compared with quiescent cells, are more dependent on glucose for their growth. Although glucose transport in keratinocytes is mediated largely by the *Glut1* facilitative transporter, **Zhang** et al. found that keratinocyte-specific ablation of *Glut1* did not compromise mouse skin development and homeostasis. Ex vivo metabolic profiling revealed altered sphingolipid, hexose, amino acid, and nucleotide metabolism in *Glut1*-deficient keratinocytes, thus suggesting metabolic adaptation. However, cultured *Glut1*-deficient keratinocytes displayed metabolic and oxidative stress and impaired proliferation. Similarly, *Glut1* deficiency impaired in vivo keratinocyte proliferation and migration

within wounded or UV-damaged mouse skin. Notably, both genetic and pharmacological *Glut1* inactivation decreased hyperplasia in mouse models of psoriasis-like disease. Topical application of a *Glut1* inhibitor also decreased inflammation in these models. *Glut1* inhibition decreased the expression of pathology-associated genes in human psoriatic skin organoids. Thus, *Glut1* is selectively required for injury- and inflammation-associated keratinocyte proliferation, and its inhibition offers a novel treatment strategy for psoriasis.

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