

The subtleties of insulin treatment in patients with lipodystrophy

Lipodistrofili hastalarda insülin tedavisinin incelikleri

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ABSTRACT

In the treatment of Diabetes Mellitus (DM), which develops on the basis of insulin resistance in patients with lipodystrophy (LD) often require high doses of insulin. Traditionally in practice is to gradually increase the insulin doses to achieve blood glucose normalization.

The fact that high insulin doses require a larger injection volume, which causes impairment in the absorption of insulin from the subcutaneous tissue to the circulation.

In this article, we discussed the clinical approach to insulin practice in the treatment of DM in patients with LD and reviewed systematically the literature.

Keywords: İnsulin treatment, lipodystrophy, concentrated insulins.

ÖZ

Lipodistrofi (LD) hastalarında insülin direnci temelinde gelişen Diabetes Mellitus (DM) tedavisinde sıklıkla yüksek doz insüline ihtiyaç duyulur. Pratikte sıklıkla uygulanan kan şekeri normalleşmesini sağlamak için insülin dozlarını kademeli olarak arttırmaktır.

Yüksek insülin dozlarının daha büyük enjeksiyon hacmi gerektirmesi, insülinin subkutan dokudan dolaşıma emiliminde bozulmaya neden olur.

Bu yazıda, LD'li hastalarda DM tedavisinde insülin uygulamasına klinik yaklaşımı tartıştık ve literatürü sistematik olarak gözden geçirdik.

Anahtar Sözcükler: İnsulin tedavisi, lipodistrofi, konsantre insülinler.

INTRODUCTION

Lipodystrophy (LD) is a rare metabolic disease characterized by congenital or acquired loss of subcutaneous fat tissue which is generalized or partial in the body and it results in metabolic complications and specific clinical findings (1).

Subcutaneous tissue is located between the skin (epidermis and dermis) and muscle. It consists of an adipose tissue that is separated into adipose lobules by a connective tissue containing collagen, elastin, glycosaminoglycan, blood vessels and lymph vessels.

The pathogenesis of lipodystrophy syndromes is not fully known, but available data suggest different pathogenic mechanisms. Among these

possible mechanisms are adipogenesis disorder due to blockade of preadipocyte-adipocyte differentiation, decreased lipid storage capacity of adipocytes, increased loss of adipocytes as a result of adipocyte apoptosis, deficiency of mature functional adipocytes or abnormal adipocytes. As a result of this pathogenesis, partial or generalized fat tissue loss occurs in the body (1, 2).

Correct insulin administration in lipodystrophy syndromes with high insulin needs has been insufficiently evaluated in the literature. The details of this subject are presented to the literature.

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Insulin resistance

Loss of adipose tissue, a functional endocrine organ, causes severe metabolic abnormalities: hyperglycemia, hyperinsulinemia, insulin resistance, Diabetes Mellitus (DM), hypertriglyceridemia, hepatosteatosis and other ectopic steatoses, endothelial dysfunction, abnormal fibrinolysis and coronary artery disease (3).

In the treatment of DM which develops on the basis of insulin resistance in patients with lipodystrophy, the need for high doses of insulin often arises. Although insulin is a hormone that has effects on many different tissues, adipose tissue is one of the organs on which insulin exerts its primary effect. It is thought that the impaired adipocyte biology in LD is the main factor that triggers the complex metabolic mechanisms of end-organ resistance against insulin. As a result of insulin resistance in adipose tissue, free fatty acids increase in plasma, which worsens insulin resistance. Ectopic fat accumulation in muscle tissue is another factor contributing to insulin resistance (4).

Traditionally in practice is to gradually increase the insulin doses to achieve blood glucose normalization. In addition, high insulin doses require a larger injection volume, which causes impairment in the absorption of insulin from the subcutaneous tissue to the circulation. So, increased insulin doses are needed in a vicious circle. Insulin absorption has been shown to

decrease with increasing injection volume and concentration (5, 6). Variability in subcutaneous absorption is an important source of glucose variability in patients using insulin and therefore an important problem in insulin therapy.

Adding the treatments for the pathogenesis of insulin resistance (metformin, thiazolidinediones-TZD-, metreleptin and insulin-like growth factor-IGF1-) to insulin therapy or using them alone can provide metabolic benefits by controlling hyperinsulinemia (7-10). GLP-1 receptor agonists (RA) reduce appetite and activate insulin signaling pathways so they are an attractive therapeutic option in patients with lipodystrophy (11). There are no published studies about usage GLP-1 RA in lipodystrophy patients, but some authors use GLP-1 agonist therapy for patients with familial partial lipodystrophy (12). It should be kept in mind that the risk of pancreatitis accompanying LD will increase with the use of GLP-1 RA. As in generalized lipodystrophy, in cases where the subcutaneous adipose tissue completely lost, the response to be obtained from treatment approaches such as TZD, which is the main treatment target adipose tissue, may be much more marginal than classical type 2 DM (3). Nevertheless, increasing insulin doses without evaluating the pathogenesis may not provide additional benefit besides increasing hyperinsulinemia in clinical practice. Insulin dose requirements reflecting insulin sensitivity are listed in Table-1 (13). However, the values defined in this table are open to discussion.

Table-1. Insulin dose requirements that reflect insulin sensitivity (13).

	Total daily insulin dose	
	U/kg	U/day
Mean insulin requirement in type 1 DM	<1	<100
Mean insulin requirement in type 2 DM	1-2	<200
High dose of insulin requirement	2-3	200-300
Very high dose dose insulin requirement	>3	>300

Insulin application and concentrated insulins

Insulin application guidelines are concerned with the possibility of lipodystrophies occurring at the sites of insulin injection but do not suggest changes in the application techniques in patients with LD (14). Insulin can be applied to the arms, legs, abdomen or buttocks. The thickness of the subcutaneous fatty tissue between the skin and the muscle in the area where insulin is applied is

important. The absorption of human insulin after subcutaneous administration is the rate-limiting step of insulin activity. In patients with LD, the most appropriate site should be recommended for injection according to examination and imaging results. Insulin made into muscle acts faster, its effect lasts shorter, but may cause severe hypoglycemia. It is the standard method to lift a large area of skin by gently pinching it

with two fingers and stick the needle vertically at a 90° angle. Injection angle can be reduced up to 45° in LD patients due to scarcity of subcutaneous adipose tissue. The waiting time, proportional to the insulin dose applied after the plunger of the pen is pressed, should be explained to the patient.

When insulin is used at very high doses, concentrated forms of insulin such as U-500 are

recommended in many studies to administer more insulin with lower volume (15, 16). However, LD patients with severe insulin resistance may not respond to concentrated insulin. The pros and cons of concentrated insulins should be evaluated in patients with LD. Concentrated insulin types and subcutaneous effect profiles are listed in Table-2 (15).

Table-2. Concentrated insulin types and subcutaneous action profiles (15).

Insulin type	Time of action (minutes)	Peak action	Duration of action (hours)
Lispro U-200	<15	30 - 90 minutes	3 - 5
Glargine U-300	90	peakless	>36
Degludec U-200	30-60	peakless	>42
Regular U-500	30	2 - 4 hours	>24
Peglispro	360	peakless	>36

The effect of insulin is conventionally demonstrated by two methods: (a) pharmacokinetic component determined by the degree and rate of absorption, distribution and clearance of insulin and (b) pharmacodynamic component determined by the metabolic effects of insulin. The structure and composition of the subcutaneous tissue play a major role in insulin absorption.

When we examine the concentrated insulins developed to reduce high volume insulin injection;

- Peglispro: The active component is insulin lispro which is linked to a large hydrophilic polyethylene glycol polymer. Peglispro is slowly absorbed after injection and also slowly cleared from circulation due to its structure. It is a hepatic specific molecule, large peglispro molecules can better access to liver tissue through windows (fenestrae) in portal vessels than to peripheral tissues, so it is effective in suppressing hepatic glucose production but has less effect on peripheral tissues, and this feature contributes hypertriglyceridemia. Peglispro has direct hepatotoxic property, failure to suppress lipolysis in peripheral tissue also contribute hepatotoxicity (17, 18).

- U-500 regular: This type of first concentrated insulin has manufactured as a concentrated form of U-100, first from bovine, then for porcine, and finally from regular human insulin. (19, 20). It is the most commonly used in patients with genetic

or acquired severe insulin resistance syndromes, and oldest concentrated form of insulin.

- Degludec U-200: Dihexamers transform into long chain multi hexamers after injection. The zinc in its structure diffuses slowly, allowing the hexamers to be separated one by one and the monomers to be released. This structure dissolves slowly and provides a slow and steady release of active insulin monomers into the circulation (17).

- Glargine U-300: It has the same amino acid sequence and metabolism as U-100, but has different absorption kinetics. Glargine U-300 has a more gradual and slow release. The storage surface of U-300 glargine is 2/3 less (21). Its use in a generalized LD patient has been reported as a case report with successful results (22).

- Lispro U-200: It has the same amino acid sequence and metabolism as lispro U100, but their absorption kinetics are different. The volume that the injection is stored in is reduced by half (23).

Continuous subcutaneous insulin infusion (CSII) pump

The fact that the basal insulin secretion in our physiology pulsates at intervals of 5-15 minutes is one of the most important factors in preventing the development of insulin resistance (24). Adjusting the basal insulin infusion rate in pulses in the continuous subcutaneous insulin infusion pump may reduce the need for insulin. Infusion

sets can be applied at an angle of 20-45° due to the scarcity of subcutaneous adipose tissue in LD patients. In cases with severe insulin resistance, infusion of U-500 insulin with the CSII pump is also recommended (25). It is stated that the deposits do not prevent absorption from the pump (26). Fiasp and Biochaperone lispro insulin are the ultra fast acting insulins which demonstrated faster appearance in venous blood (4 min.) after subcutaneous administration. They are effective in infusion with the CSII pump, in hypothesis fast absorption rates can make them suitable for use in LD patients with CSII pump (27).

CONCLUSION

Concentrated insulins are therapeutic tools that make diabetes treatment perfect when used in the right patient. However, in LD patients with subcutaneous adipose tissue deficiency, the use of concentrated insulins with slow absorption by storage in subcutaneous tissue does seem

hypothetically challenging due to the limitation of storage space. On the other hand, since the volume of the injection is reduced with concentrated insulins, this time, it may be an advantage in the absence of subcutaneous adipose tissue. Final results should be reported by conducting comparative studies of both basal and prandial concentrated insulins with U-100 insulins in LD patients. It will be more scientific to discuss with these results.

Compliance with Ethical Standards

Authors declare no potential conflicts of interest, whether of a financial or other nature.

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