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Insulin-induced lypodistrophy in hemodialyzed patients: A new challenge for nephrologists?

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ABSTRACT

Diabetes Mellitus (DM) is the most common cause of renal failure and ESRD all over the world, and often requires an individualized insulin treatment regimen. Malnutrition, depression-related eating behavior changes, high on-off-dialysis day-to-day glycemic variability and frequent hypoglycemic events occurring during or immediately after dialysis make it hard to identify best insulin dosage in hemodialyzed patients. This suggests a prudent attitude including non-stringent control, despite which repeated hypoglycemia quite often occurs in such patients. When looking for possible sources of hypoglycemia, health professionals too often overlook the identification of skin lipodystrophy (LD) due to an incorrect insulin injection technique. This mini-review focuses on the high frequency (57%) of LD in a cohort of 1004 insulin-treated people with DM on dialysis consecutively referring to our joint medical centers, and on its relationship with hypoglycemia and glycemic control/variability. When taking on such patients, care team members accept to face a complex disease burdened with several risk factors requiring high professional skills, and have to keep in mind also the possible presence of any LD areas eventually interfering with expected results. A timely educational intervention on the correct injection technique can help reduce the high risk of hypoglycemia and large glycemic variability in dialysed people with DM.

1. Introduction

Insulin is necessary for carbohydrate, protein, and fat metabolism. People with diabetes mellitus (DM) either do not produce enough of it to sustain life and therefore depend on exogenous supply for survival - which is the case for type 1 DM (T1DM) — or produce sufficiently high amounts of less active insulin to survive — which is the case for type 2 DM (T2DM) - but over the years, and especially in case of stress or intercurrent illness making insulin secretion insufficient, often require exogenous administration for adequate blood glucose control.

2. Diabetes and end stage renal disease

An insulin regimen is often required in the treatment of several comorbidities, such as end stage renal disease (ESRD). Whenever insulin is needed, its dosage must be individually customized to nutrition and exercise habits. DM is the most common cause of renal failure and ESRD all over the world so that people with ESRD quite often have insulin requiring DM as a result of either severe deficiency or alternative drug contraindications [1].

Various factors make it difficult to establish optimal insulin doses in the hemodialyzed patient, including malnutrition, depression-related eating behavior changes, high on-off-dialysis day-to-day glycemic variability and increased hypoglycemic risk during or immediately after dialysis. For these reasons it is suggested to keep glycemic control within HbA1c values 7.5%—8.5% [2].

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3. Insulin and lipohypertophy

Since insulin commercialization skin lipodystrophy (LD) - predominantly atrophic (LA) - has been described at injection sites [3–6]. Initially its etiology was not understood but we now know they depended on both inner lipo-active insulin properties and on immuno-allergic, inflammatory reactions due to impurities contaminating animal extracts [7,8].

Today the most frequent type of LD is lipo-hypertrophy (LH), which is due to (i) non-compliance to injection site rotation suggestion, (ii) too long and (iii) often reused needles, (iv) especially when repeatedly inserted into the same site within restricted skin areas, and, (v) the utilization of ice-cold insulin [8].

4. Statements and recommendations

Various Expert Forums have been organized so far all over the world to collect evidence from the literature on how to prevent and/or treat LD [9–14].

In addition, for years several Scientific Societies have been issuing consensus statements, and National Expert Groups have been producing recommendations and guidelines on proper injection techniques to prevent LD from resulting into poor metabolic control [15–23]. However, with somewhat different frequency distribution among reports (most likely dependent on discrepancies in identification methods) [24–26], LD occurrence rates still keep higher than 50% and get mostly up to 1/3 cases in insulin-requiring patients world-wide.

5. Real life

Despite excellent results of adequate education [17,27,28], the best frequency of periodic refreshers needed to maintain a correct injection technique over time remains unknown. In addition, the largest difference between clinical practice observations and educational trial results is the direct consequence of unabated LD rate worldwide despite easily available guidelines/recommendations and ever improving high-tech administration devices.

The most relevant consequences of that [8,28] are unpredictable hypoglycemia and large glycemic variability, both of which depend on either erratic insulin release and absorption from fibrous and edematous areas (in case of LH occurrence) [29] or on unexpectedly high insulin amounts massively entering the blood stream (in case of LA) [30]. In fact LH deteriorates metabolic control and quality of life, thus paving the way to acute and chronic complications and sharply increasing health-related costs [31] as independent factors of increased cardiovascular (CV) risk, all-cause mortality and hospitalization [32].

6. Insulin treatment and ESRD

All patients on hemodialysis are at high risk for CV events and higher mortality rate as a result of the often associated comorbidities including DM, and therefore get even frailer whenever the deleterious metabolic effects of LD happen to further increase CV risk. That's why LD identification and timely refreshers on correct injection techniques are crucial for their survival. In the first observational study specifically oriented to 1004 insulin-treated hemodialyzed patients referring to our joint medical centers, we found as high as 57% LH lesion rates, not dissimilar to those found in insulin-treated DM patients without ESRD [33]. This came with poorer glycemic control (HbA1c) (Fig. 1) in patients with LHs than those without LHs together with a significantly higher frequency of needle reuse (Fig. 1) and HYPOs (severe/non severe) (Fig. 2), as well as, a wider glycemic variability (Fig. 3).

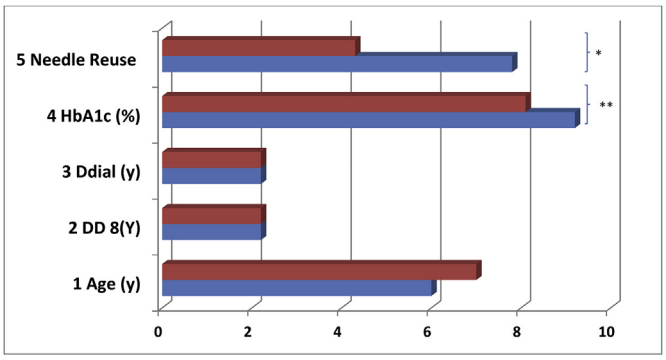

Fig. 1. Quantitative independent variables grouped by LH presence (n.169, blue bars)/absence (n.127, red bars), and significant differences in a series of 296 dialysis patient with insulin-treated diabetes out of 1004 dialyzed patients: *1) Age (y) p n. s.; 2) Diabetes Duration (y) p n.s.; 3) Dialysis Duration (y) p n.s.; 4) HbA1c (%) p < 0.007**; 5) Needle reuse (frequency) p < 0.029*.*

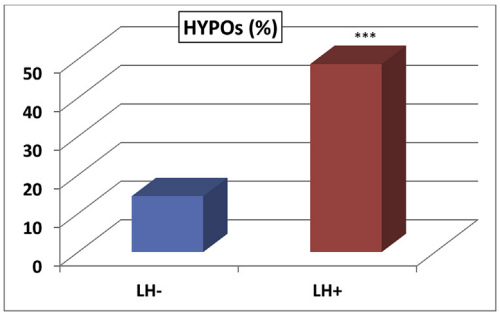

Fig. 2. Mean rates of severe/non severe hypoglycemia (HYPOs %) in patients without LH (LH-) and with LH (LH+) over three months: p < 0.0001 (***).

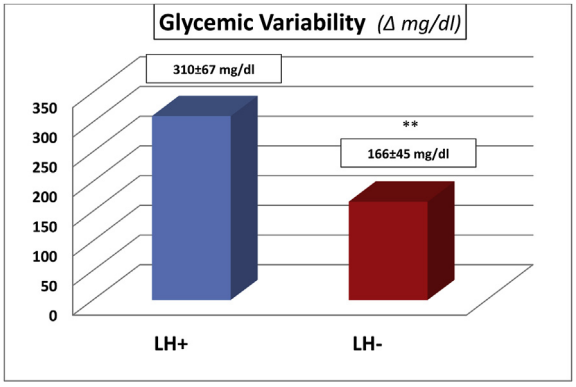

Fig. 3. Glycemic variability (mg/dl), calculated as means of day-do-day variability. between days on and off dialysis: p < 0.007 (**).

7. A new challenge for medical teams

Therefore, when taking on patients with diabetes and ESRD needing dialysis, the nephrologist and all his team accept to face a complex disease burdened with several risk factors requiring high professional skills. They must keep in mind all patient's comorbidities and, when trying to dampen glycemic variations observed among days on and off dialysis or between the time of dialysis and the one immediately before/after dialysis, they must also rule out the presence of any LH areas eventually interfering with expected results.

8. Future perspectives

LH identification represents a new challenge for the nephrologist, who in turn can experience the great satisfaction of significantly improving not only glycemic control, but also the outcome of all comorbidities and the overall prognosis of their DM patients on long-term dialysis.

Authorship

SG and FS laid out the paper plan and wrote the manuscript. ES, TDC and GG critically read the paper. All Collaborators (see the List of Members of the Nefrocenter Research Study Group, Reference n. 33) complied with data collection, critically assessed the results and approved the final text.

Ethical standards

This study was conducted in conformance with good clinical practice standards. The study was led in accordance with the Declaration of Helsinki 1975, as revised in 2008, and was approved by all the Ethics Committees of the Centers participating in the study.

Human and animal rights

All followed procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national).

Informed consent

Written informed consent was obtained from all participants before enrollment.

Declaration of competing interest

The authors declare no conflicts of interest.

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