Diabetes & Metabolic Syndrome: Clinical Research & Reviews INSULIN-INDUCED SKIN LIPOHYPERTROPHIES: A NEGLECTED CAUSE OF HYPOGLYCEMIA IN DIALYSED DIABETIC SUBJECTS

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11 authors, including:

Ersilia Satta
NefroCenter Research

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# Insulin-Induced Skin Lipohypertrophies: A Neglected Cause of Hypoglycemia in Dialysed Diabetic Subjects

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**Corresponding Author:** Teresa Della Corte  
Università di Napoli Luigi Vanvitelli, Dipartimento di Internistica Clinica e Sperimentale ITALY

**First Author:** Teresa Della Corte

**Order of Authors:** Teresa Della Corte  
Ersilia Satta  
Felice Strollo  
Carmine Romano  
Carmelo Alfarone  
Giuseppina Guarino  
Sandro Gentile

**Abstract:** Diabetes is the leading cause of end-stage renal disease (ESRD) and dialysis, that remains the most frequent complications of diabetes itself. Medicare expenditures for both diseases are quite high. The risk for hypoglycemia and its related CVD complications is increased when eGFR is <60 ml/min/1.73m² (i.e., in people with ESRD and dialysis). Greater attention to that is needed in older patients with ESRD, for whom therapeutic approach is mainly based on insulin, and special care has to be taken in individualizing treatment targets in both the intra- and inter-dialysis timeframes, and to avoid dangerous hypoglycemias (HYPOs). The risk of both HYPOs and large glycemic variability (GV) is also strictly related to improper injection techniques. Such errors generate cutaneous lipohypertrophy (LH) affecting about 50% patients, and strongly related to unpredictable HYPOs and large GV, thus increasing the already high risk of cardiovascular complications, and care expenditure. Because of that, all health professionals working in dialysis units should be trained in preventing LH development and progression to try and get rid of such avoidable complication, which represent an additional metabolic burden to the already high ESRD-related quality of life disrupting potential.

**Suggested Reviewers:**

ANDRES FRID  
dr.frid@telia.com

KENNETH STRAUSS  
Kenneth_Strauss@Europe.bd.com

ANNA NOVIALS  
Diabetes and Obesity Research Laboratory and Adjunct Scientific Director, CIBERD  
anovials@clinic.ub.es

ANTONIO CERIELLO, MD, PhD  
Director, IRCCS Multimedica- Italian Ministry of Health, Cardiology and Cardiovascular Science, Milan, Italy  
antonio.ceriello@hotmail.it

SALVATORE DE COSMO, MD, PhD  
Director  
sdecosm@tin.it  
Director of Complex Structure of Endocrinology and Diabetology and Director of the Department of Medical Sciences Hospital, Foggia, Italy
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>M GALLO, MD, PHD</td>
<td>DIRECTOR</td>
<td><a href="mailto:mgallo4@cittadellasalute.to.it">mgallo4@cittadellasalute.to.it</a></td>
</tr>
<tr>
<td></td>
<td>Endocrinologist</td>
<td></td>
</tr>
<tr>
<td>TUULA MARIA PARTANEN</td>
<td>North-Savo Polytechnic, School of Social and Health Professions, Kuopio, Finland</td>
<td><a href="mailto:tuulamaria.partanen@pspt.fi">tuulamaria.partanen@pspt.fi</a></td>
</tr>
<tr>
<td>MARIO MASONE, MD</td>
<td></td>
<td><a href="mailto:MARIO.MASONE@GMAIL.COM">MARIO.MASONE@GMAIL.COM</a></td>
</tr>
<tr>
<td>GIUSEPPINA RUSSO, MD</td>
<td></td>
<td><a href="mailto:GIUSEPPINA.RUSSO@UNIME.IT">GIUSEPPINA.RUSSO@UNIME.IT</a></td>
</tr>
<tr>
<td>DOMENICO CUCINOTTA, MD</td>
<td>Universita degli Studi di Perugia Dipartimento di Medicina Sperimentale</td>
<td><a href="mailto:DOMENICO.CUCINOTTA@UNIME.IT">DOMENICO.CUCINOTTA@UNIME.IT</a></td>
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**Opposed Reviewers:**
Dear editor-in-chief,

I have the pleasure of submit as a corresponding author the short communication entitled “INSULIN-INDUCED SKIN LIPOHYPERTROPHIES: A NEGLECTED CAUSE OF HYPOGLYCEMIA IN DIALYSED DIABETIC SUBJECTS” for publication in Diabetes & Metabolic Syndrome: clinical research & reviews. Diabetes is the leading cause of end-stage renal disease (ESRD) and the costs expected for both diseases are quite high and further aggravated by hypoglycemic episodes (HYPO) and marked glycemic variability (GV) which, in turn, increase mortality rate. Insulin is the treatment of choice for ESRD but entails a high risk for Hypos and GV, especially when injected into a skin area home to lypohypertrophy (LH), the staff of dialysis unit should therefore be carefully trained to prevent LH development and progression.

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

All authors have approved the manuscript and agree with its submission to diabetes & metabolic syndrome: clinical research & reviews.

We look forward to hearing from you at your earliest convenience.

with my best regards,

sincerely yours,

Teresa Della Corte, MD
Campania University “Luigi Vanvitelli”, Naples, Italy
e-mail: tere.dellacorte@gmail.com
HIGHLIGHTS:

- Diabetes is the leading cause of end-stage renal disease (ESRD);
- Costs expected for both diseases are quite high and further aggravated by hypoglycemic episodes (HYPO) and marked glycemic variability (GV) which, in turn, increase mortality rate;
- Insulin is the treatment of choice for ESRD but entails a high risk for Hypos and GV, especially when injected into a skin area home to lypohypertrophy (LH);
- The staff of dialysis unit should therefore be carefully trained to prevent LH development and progression.
INSULIN-INDUCED SKIN LIPOHYPERTROPHIES: A NEGLECTED CAUSE OF HYPOGLYCEMIA IN DIALYSED DIABETIC SUBJECTS

Ersilia Satta¹, Felice Strollo¹,², Carmine Romano¹, Teresa Della Corte¹,³, Carmelo Alfarone¹,⁴, Giuseppina Guarino³ e Sandro Gentile¹,³

¹Nefrocenter Research Network & Nyx Innovative Research Start-Up, Naples Italy
²Endocrinology and Diabetes, San Raffaele Pisana Research Institute, Rome, Italy
³Department of Internal Medicine, Campania University “Luigi Vanvitelli”, Naples, Italy,
⁴Diagtest Dialysis Unit, Rome

Summary

Diabetes is the leading cause of end-stage renal disease (ESRD) and dialysis, that remains the most frequent complications of diabetes itself. Medicare expenditures for both diseases are quite high. The risk for hypoglycemia and its related CVD complications is increased when eGFR is <60 ml/min/1.73m² (i.e. in people with ESRD and dialysis). Greater attention to that is needed in older patients with ESRD, for whom therapeutic approach is mainly based on insulin, and special care has to be taken in individualizing treatment targets in both the intra- and inter-dialysis timeframes, and to avoid dangerous hypoglycemias (HYPOs). The risk of both HYPOs and large glycemic variability (GV) is also strictly related to improper injection techniques. Such errors generate cutaneous lipohypertrophy (LH) affecting about 50% patients, and strongly related to unpredictable HYPOs and large GV, thus increasing the already high risk of cardiovascular complications, and care expenditure. Because of that, all health professionals working in dialysis units should be trained in preventing LH development and progression to try and get rid of such avoidable complication, which represent an additional metabolic burden to the already high ESRD-related quality of life disrupting potential.

Key words: diabetes, lipohypertrophy, injection technique, hypoglycemia, diabetic nephropathy

Corresponding author: Teresa Della Corte: tere.dellacorte@gmail.com
The incidence and prevalence of diabetes mellitus (DM) have grown significantly for the last ten years or so all over the world, mostly in terms of type 2 (T2DM) rather than type 1 (T1DM). This has had a major impact, in turn, on the number of people developing diabetic kidney disease (DKD) (1).

However, both DM and different types of kidney disease are frequent chronic conditions also occurring independently of each other, so that patients may have chronic kidney disease (CKD) as an add-on to, rather than a complication of DM. Apropos of that it is also important to note that DKD remains one of the most frequent complications of both T1DM and T2DM which are the leading causes of end-stage renal disease (ESRD) in developed countries by accounting for approximately 50% of cases. Although incidence rates for ESRD attributable to DKD have stabilized over the past few years (2,3), differences remain among high-risk subgroups with middle-aged African Americans, Native Americans, and Hispanics still having higher rates of ESRD than other clusters. The above-mentioned health disparities may be linked, in part, to the increasing rates of obesity and T2DM observed in young subjects from these populations allowing for the development of DM complications earlier in life (4).

The overall costs for care for people with DKD are extraordinarily high, largely depending on the strong relationship linking DKD to cardiovascular disease (CVD) and ESRD (3). For example, overall expenditures for diabetes and CKD in the Medicare population were approximately $25 billion in 2011 and mostly went on over65s. Referring to the latter, the per person per year costs were $20,000 at the transition to ESRD for people covered by Medicare versus $40,000 calculated for patients <65 years of age. Albuminuria and glomerular filtration rate (GFR) independently and additively associate with all-cause and CVD mortality according to a positive and negative function, respectively, and, in fact, most of the excess CVD prevalence in DM is accounted for by the those with DKD (4).

Risk of hypoglycemia is increased when eGFR is <60 ml/min/1.7m² (i.e. in people with CKD). This is partly due to the decrease of both kidney-related gluconeogenesis and clearance rate of hypoglycemic agents (6,7). Dose adjustments are therefore required for many hypoglycemic agents when used in people with DKD. Insulin clearance rate decreases in parallel with a decline in eGFR (6-8). As with insulin use in general, frequent self-monitoring of blood glucose and appropriate patient-specific dose titration are critical to achieve individual treatment goals and avoid hypoglycemia (6-8). With respect to that, special attention has to be paid to the fact that, after initiated on long-term dialysis treatment, patients often require less exogenous insulin due to the onset of malnutrition (6). Moreover, older individuals are at greater risk for HYPOs and for adverse consequences from HYPOs per se (9,10). Therefore, greater care to avoid HYPOs is needed and less stringent HbA1c treatment targets are recommended in the older patient with DKD (11).

Due to the markedly reduced GFR entailed by renal failure, in patients on dialysis only few DM-related medications are recommended including insulin which, however, being burdened by a high risk of HYPO, requires a substantial dose reduction over time (13,14). In fact, despite being mostly asymptomatic, HYPOs occur quite often in dialyzed people as a result of various factors including not only glucose lowering drugs but also diet errors, prolonged fasting, alcohol intake, chronic malnutrition, malignancies, heart/hepatic/renal failure, adrenal or thyroid hormone deficiency, beta-blockers or other drugs.

The HYPO risk increases in advanced DKD patients transitioning to dialysis, and the rate of severe HYPOs further increases after initiating dialysis, with a strong association with one-year mortality (15). In fact, as well known to nephrologists, a marked intra-/between-day glycemic variability (GV) further increasing HYPO-related CVD risk results from intermittently enhanced insulin clearance rate in patients on dialysis (14, 16-20).
In greater detail, among advanced DKD patients, HYPO risk progressively increases during the critical dialysis transition period. Increased frequency of severe HYPO-related hospitalizations is associated with higher mortality risk one year after transitioning to dialysis. Factors strongly associated with HYPO risk are hematocrit compared to peritoneal dialysis, stroke, use of insulin (15).

Glucose variability, i.e. the occurrence of several episodes of hyper- and hypoglycemia within a relatively short period, is a challenge for all insulin-treated patients, especially those with T1DM and/or ESRD or on chronic hemodialysis. Despite the fact that clinicians mostly focus on the type and amount of insulin to cope with glucose intake when reviewing their patients’ glucose logs or meter downloads, at least as important is appropriate insulin injection technique [IT].

Insulin pharmacokinetics [PK] are derived from carefully controlled studies on healthy subjects at rest. In the clinical world, however, many factors affect PK, including whether insulin is delivered into Subcutaneous (SC) fat or as an intramuscular injection (IMI).

SC route is used for insulin delivery because expected to ensure much more consistent hormonal absorption rates than IMI. Nevertheless, being too long than needed, many needles commonly used with insulin pens and syringes are now known to increase the risk for IMI injections which, in fact, may markedly and unpredictably increase in insulin uptake depending on whether the muscle is at rest or exercised (21). To minimize this risk, patients are often taught to lift skinfolds or at least to angle the needle by 45°. A more practical approach is to simply switch patients to shorter needles.

Another concern of improper IT is the development of lipohypertrophy (LH). LH has been shown to affect several insulin self-injecting patients (22-26) (Figures 1-3). Improper injection site rotation and needle reuse are the most common factors associated with LH. Injecting into LH reduces insulin absorption and action thus allowing postprandial glucose to sharply increase, and causes highly variable insulin uptake (26).

Despite this, inspection of injection sites is not routinely performed by health care professionals (HCPs) or patients, hence the "unexplained" nature of many blood glucose fluctuations.

Approximately half a billion people in the world have diabetes (27). All people with type 1 diabetes and around 20-25% of those with type 2 diabetes use insulin, mostly through repeated daily injections. Worldwide insulin users are estimated to be as many as 150-200 millions (28).

Despite being the most effective glucose-lowering medication for diabetes, insulin has one of the lowest therapeutic indexes among medications and is regularly attributed a high risk or high alert by the Institute for Safe Medications Practices (29). This risk can be further increased by improper IT.

LH is the most frequent local complication of both insulin injections (22-26,30) and pump infusions (31,32) with some 50% prevalence rates according to multiple studies from various countries (30). HCPs taking care of insulin-injecting patients should make it a habit to check for LH frequently (at least yearly), especially in patients with high GV and unexplained HYPOS. As mentioned before, when injected into LH lesions, insulin results in delayed or erratic absorption (PK), which adversely affects its action (i.e. pharmacodynamics, PD) and glycemic control as a direct consequence of that (33-36).

A recent crossover glucose clamp study demonstrated that both insulin PK and PD are blunted with injection into LH areas, with 3-5 times greater variability than observed at equal doses into normal areas. A controlled mixed-meal tolerance test in the same study showed prolonged hyperglycemia after injection into LH lesions as well (26). The key message here is that insulin should never be injected into LH areas. In addition, patients affected with LH require significantly higher insulin daily doses than patients without LH (22,24), and higher
LH-related insulin doses lead to substantially increased direct costs for patients or payers. When patients shift from injecting insulin into LH and start using normal tissue, HYPO risk, as well as, GV, daily insulin requirement and related cost consistently decrease (22, 25, 37).

In a recent multicenter observational study, focusing upon LH identification at insulin self-injection sites in a large series of dialyzed diabetic subjects, for the first time to our knowledge we described that over 50% of ESRD/dialyzed patents have LH due to inappropriate IT, including missing injection site rotation, as well as, too long needles and too small skin areas chosen for injections (38).

Particularly relevant for hemodialyzed insulin-treated patients with LH lesions is the damage caused by LH-dependent increases in GV and HYPO prevalence rate, as compared to those already expected from periodic on/off dialysis switches: education to correct IT would markedly decrease GV, HYPO risk and diabetes costs in such clinical set too (22,23,25).

In conclusion, as great GV and frequent symptomatic/severe HYPOs are independent risk factors for CV, all-cause mortality, and hospitalization (39-43), we strongly believe that future investigations concerning HYPO risk patients on dialysis should never forget the great contribution to that risk provided by LH occurrence and from now on all health professionals working in dialysis units should be trained to prevent LH development and progression to set patients free from the additional metabolic burden further disrupting their ESRD-related intrinsically poor quality of life.

**Conflicts of Interest**

None of the authors has conflicts of interest to declare

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**Authorship**

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published: Sandro Gentile, Giuseppina Guarino, Teresa Della Corte, Ersilia Satta, Carmine Romano e Carmelo Alfarone, and Felice Strollo

**Authorship Contributions**

SG and FS created the paper and wrote it. ES, TDC, GG, CA, CR, critically read and approved the paper. All approved the final text. All Collaborators critically read and approved the final text.

**Compliance with Ethics Guidelines**
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 2013, and was approved by Vanvitelli University, Naples, Italy. Written informed consent was obtained from all patients before publishing their photos.

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**Compliance with ethics guidelines**

This article is based on previous conducted studies and does not contains any studies with humans participants or animals performed by any of the authors.

**References**


**Figure 1.** Lipohypertrophy clearly visible in the proximal forearm, an abnormal injection site.

**Figure 2.** Symmetrical lipohypertrias on the sides of the navel; the right is larger.
Figure 3. Large flat lipohypertrophy in the lower part of the abdomen, just visible but well palpable with the pinching maneuver. The affected skin is thicker than normal, and is more pasty.
CONFLICT OF INTEREST

I Sandro Gentile  Campania University “Luigi Vanvitelli”, Naples, Italy,  and Nefrocenter Research & Nyx Start-UP Study Group Coordinator

DECLARE:

It is not, to your knowledge, nor you nor the study participants, direct or indirect interests in the pharmaceutical industry

In the case of the Public Interest And On The Commission, it is important to note that there is a need for a new public declaration of interest.

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Naples, 06/05/2020
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