

XXIII CONGRESSO NAZIONALE AMD

UNA NUOVA DIABETOLOGIA TRA SOSTENIBILITÀ,
PROSSIMITÀ E INNOVAZIONE



Bologna

27/30 Ottobre 2021

Bologna Congressi - Volvo Congress Center

Simposio AMD - ANIAD - OSDI 100 anni di insulina e di lipodistrofie: un problema irrisolto

SANRO GENTILE

INTRODUZIONE





MILESTONES DELL'INSULINA

1869: Paul Langerhans identifica piccoli isole di cellule per la regolazione della digestione.

1916: Paulescu inietta nel cane diabetico una soluzione estratta dal pancreas

1921: Banting e Best isolano l'isletina, e ne testano l'effetto su cani diabetici.

1922: estrazione dell'insulina dal pancreas bovino e trattato il primo paziente.

1922: August Krogh e la moglie Marie producono l'insulina in Europa.

1923: premio Nobel a Banting e Macleod

1925: l'insulina è commercializzata.

1935-1936: sviluppo della prima insulina zinco-protaminata che dura fino a 24 ore.

1946: introdotta l'insulina a PH neutro di durata intermedia (12 ore, Hagedorn)

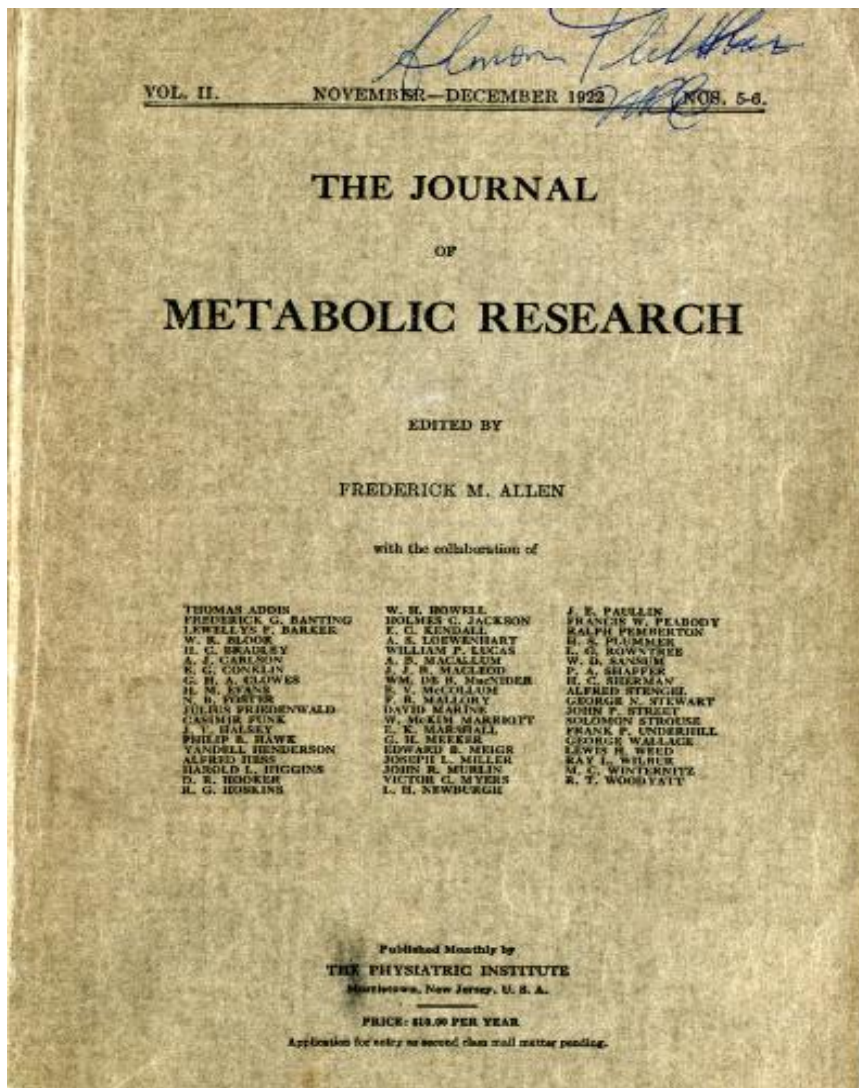
1954: Frederick Sanger e collaboratori scoprono la struttura molecolare dell'insulina

1955. A Sanger va il Premio Nobel per la Medicina

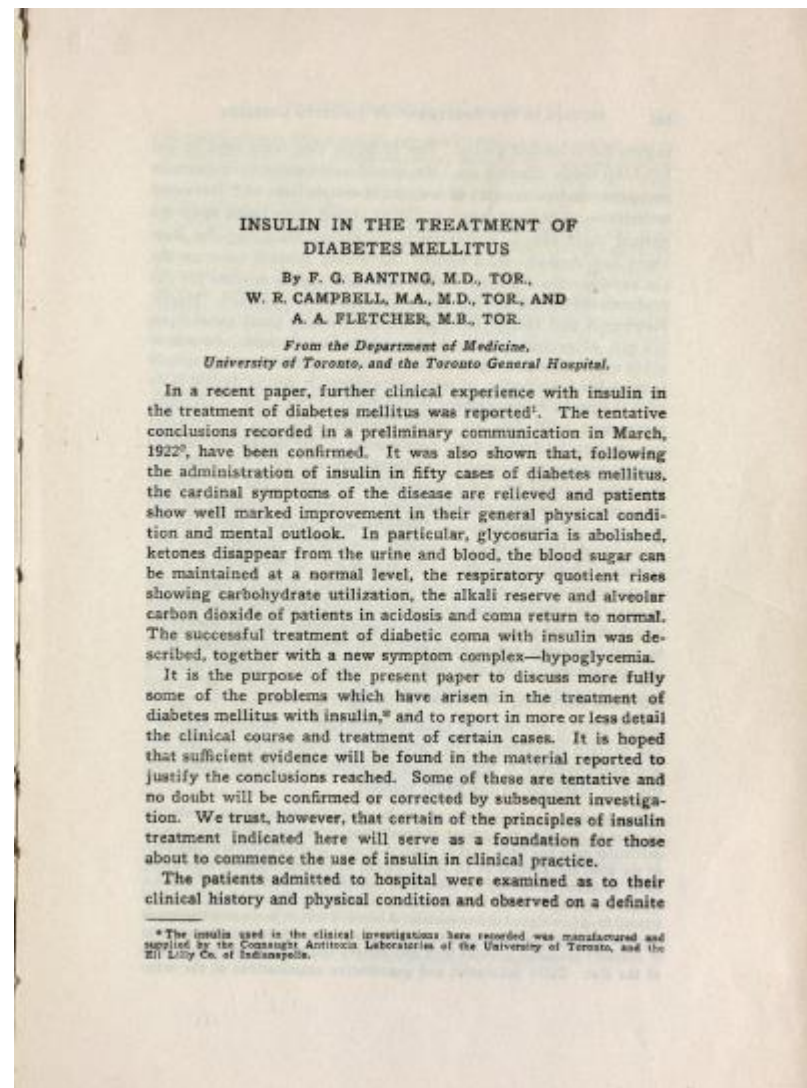
1968-1970: insulina monocomponente pura (MC), che riduce il rischio di risposta immunitaria

1982: prima insulina umana biosintetica da DNA ricombinante

1999: la prima insulina umana veloce iniettabile subito prima dei pasti.



1922





I MEDIA E LA SCOPERTA DELLA CURA DEL DIABETE



Soon after its discovery, insulin captivated media attention (Banting Digital Library)



Lipoatrophy following the injection of insulin

Williams J. R.

Journal of Metabolic Research 1922;2:729

PRIMA NOTIZIA DI LIPODISTROFIA

TESTO NON REPERIBILE



- 1922** - Williams J. R.: Lipoatrophy following the injection of insulin. *J Metabol Resh*;2:729.
- 1923** - Bowie, DJ, Robinson, WL. Histological Study of Muscle Degeneration Produced by Local Injections of Insulin, *J. Lab. & Clin* 8:569
- 1926** - C.J. Fatty atrophy from injections of insulin: report of two cases. *J Am Med Assoc*;87(20):1646-1647. <https://doi.org/10.1001/jama.1926.92680200003012c>.
- 1926** - Depisch F. Über lokale lipodystrophie bei lange zeit mit insulin behandelten fallen von diabetes. *Klin Wochenschr* 5: 1965 (oct 15).
- 1928** - Priesel R, Wagner R. Über lokale lipodystrophie nach insulininjectionen. *Ztschrif. Kinderh.* 46:453 (4)
- 1927** - Davidson RA. Absorption of subcutaneous fat deposits at site of repeated insulin injections. Report of case. *Calif West Med*;26(2):210-2.
- 1928** - Barborka I, Rabinowitch M, Atrophy of subcutaneous fat following insulin injection. *Canad M A J* 18:560 (28)
- 1928** - *Carmichael, E. A., and Graham, G.*: Local Fat Atrophy Following Insulin. Injections, *Lancet* 214:601 (March 24)
- 1928** - Graham, Lipoatrophy following the injection of insulin. *Lancet*, , 214, 601.
- 1929** - Fischer AE, The frequency of Atrophy of the subcutaneous fat following the injection. *Am J Dis Child* 38:715 (oct)
- 1929** - Avery H. Insulin fat atrophy: a traumatic atrophic panniculitis. *Brit M J* 1:597.
- 1949** - Collens WS, Boas LC, et al. Lipoatrophy following the injection of insulin; a method of control. *N Engl J Med* 241:610-611



15. OKTOBER 1966

KLINISCHE WOHENSCHRIFT. 5. JAHRGANG. Nr. 42

1965

**ÜBER LOKALE LIPODYSTROPHIE BEI LANGE
ZEIT MIT INSULIN BEHANDELTEN FÄLLEN
VON DIABETES*).**

Von
Dr. F. DEPISCH,





ATROPHY OF SUBCUTANEOUS FAT FOLLOWING INSULIN INJECTIONS*

BY I. M. RABINOWITCH, M.D.

Montreal

These local reactions appear to lead to no general physiological disturbance, except when insulin is injected into the indurated masses. When this is done, the absorption, and therefore the action, of insulin is slow, or it may fail to act completely. This complication is readily overcome by frequently altering the sites of injection.



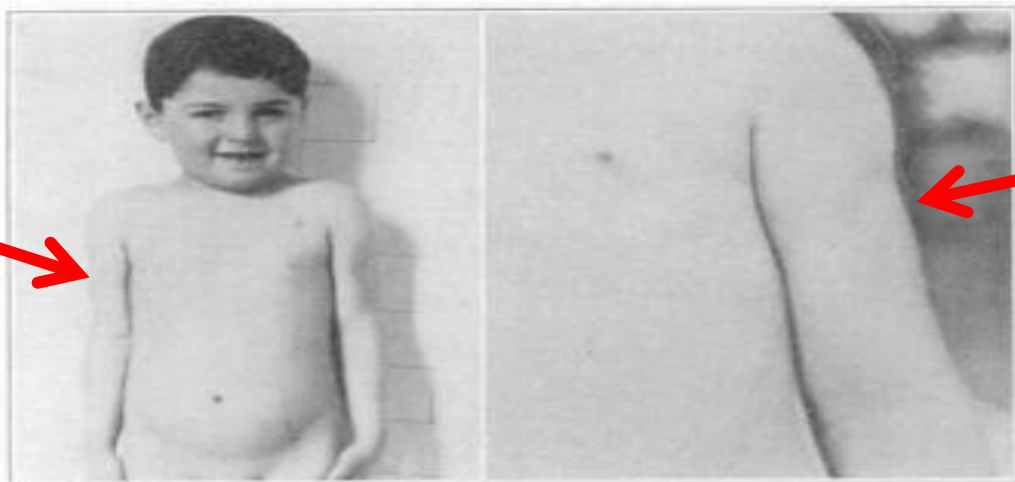
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AMERICAN JOURNAL OF DISEASES OF CHILDREN

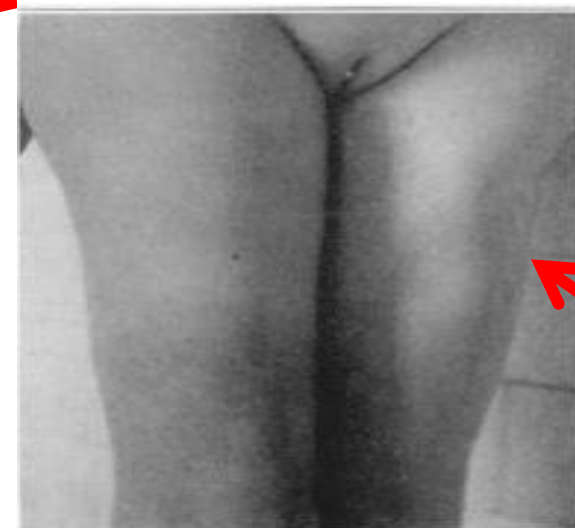
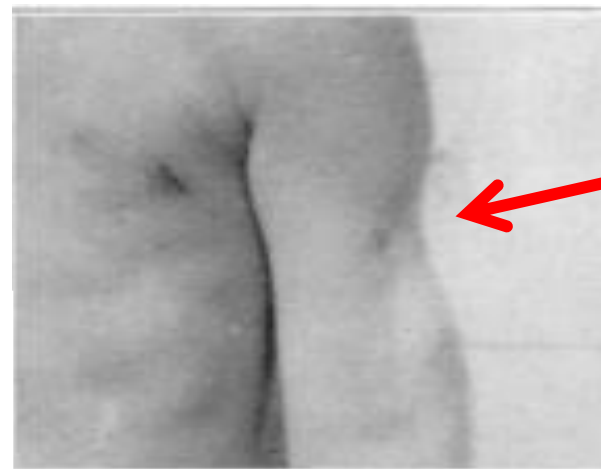
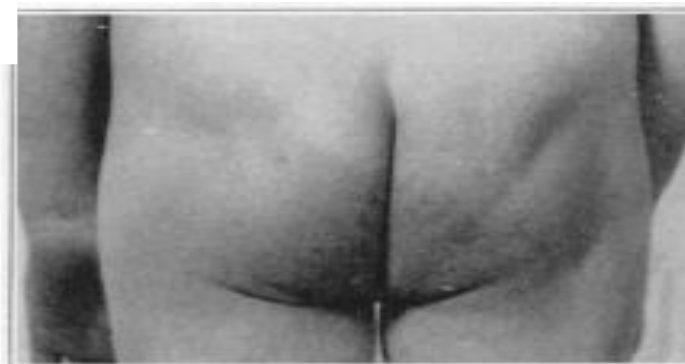
1929

THE FREQUENCY OF ATROPHY OF THE SUBCUTANEOUS FAT FOLLOWING THE INJECTION OF INSULIN *

ALFRED E. FISCHER, M.D.
NEW YORK



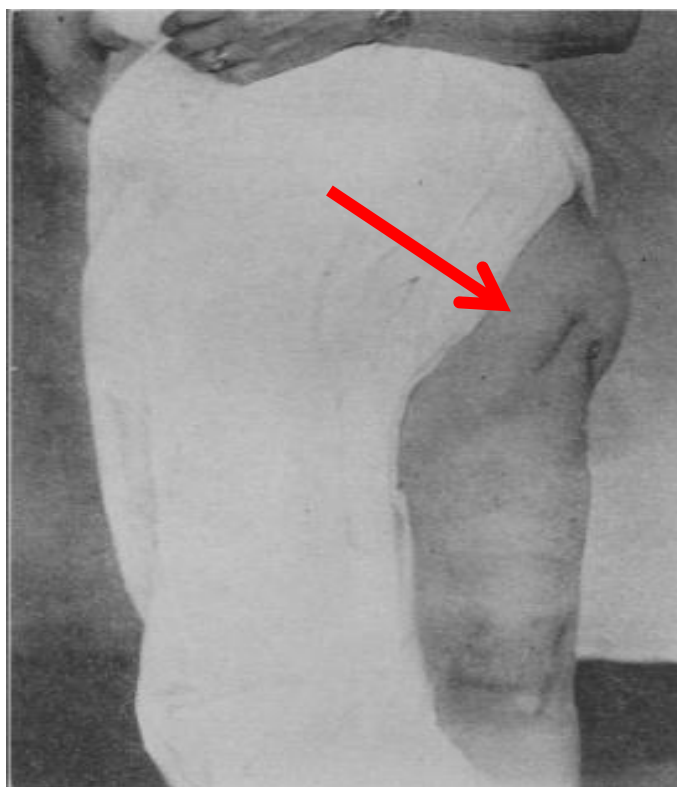
of the subcutaneous fat of both arms; B,



ABSORPTION OF SUBCUTANEOUS FAT DEPOSITS AT SITE OF REPEATED INSULIN INJECTIONS

REPORT OF CASE

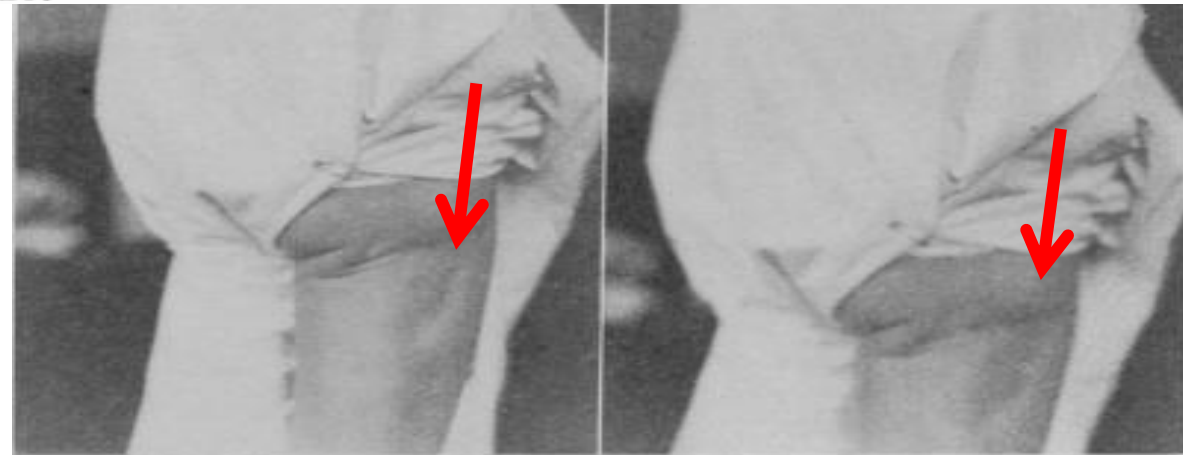
By ROLAND A. DAVISON *



SINCE the introduction of insulin for use in treatment of diabetes mellitus, numerous workers have reported sensitization phenomena, including urticarial wheals and indurations at the site of subcutaneous injections, serum sickness, and general anaphylactic symptoms. Williams,¹ Geyelin,² Wilder,³ Gibson and Larimer,⁴ Raynaud and La Croix.⁵

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1. Williams, J. R.: *Journal of Metabolic Research*, 2, 729, 1922.
2. Geyelin, H. R.: *Journal of Metabolic Research*, 2, 767, 1922.
3. Wilder, R. M.: *Journal of Metabolic Research*, 2, 701, 1922.
4. Gibson and Larimer: *Journal of the A. M. A.*, 84, 491-2, 1925.



LIPODYSTROPHY FROM INSULIN INJECTIONS *

LUCILLE L. REED, PH.D.

WILLIAM E. ANDERSON, M.A.

AND

LAFAYETTE B. MENDEL, PH.D.

NEW HAVEN, CONN.

Since 1926, when Depisch¹ in Germany and Barborka² in America described the disappearance of fat from the subcutaneous tissues of several diabetic patients at the site of insulin injections, a number of reports have been made of this condition and many speculations have arisen as to its cause.

LIPOTROPHY FOLLOWING THE INJECTION OF INSULIN*

A Method of Control

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THE NEW ENGLAND JOURNAL OF MEDICINE

Oct. 30, 1949

LIPOTROPHY FOLLOWING THE INJECTION OF INSULIN*

A Method of Control

WILLIAM S. COLLENS, M.D.,† LOUIS C. BOAS, M.D.,‡ JAMES D. ZILINSKY, M.D.,‡ AND
JEROME J. GREENWALD, M.D.‡

BROOKLYN, NEW YORK

AMONG the many problems that have arisen since insulin was introduced as an agent in the treatment of diabetes mellitus is one concerned with the development of local fat atrophy at the site of insulin injections. Although of relatively infrequent occurrence, the problem has always proved to be very distressing to the patient because of the considerable amount of disfigurement it produces.

Insulin lipotrophy is a condition in which the subcutaneous fat disappears at the site of the insulin injection, leaving a depression in the skin (Fig.

considered responsible are the crystals used as a preservative of insulin, alcohol and its derivatives used in sterilizing syringes and needles, injury to fat cells following the introduction of the hypodermic needle, possible lipolytic ferments present in insulin and possible nerve injury.

On the basis of the possibility that this condition might be an allergic phenomenon, some of the patients in our clinic were subjected to skin tests by the intradermal injection of various commercial brands of insulin. There was no uniformity in the reaction, some being negative and others mildly



A



B

FIGURE 1. Case of Insulin Lipotrophy Involving Both Arms.
A shows appearance before treatment. B shows appearance two months after treatment of the left arm. (Note the marked improvement; the right arm was used as a control and was not treated.)

1 and 2). It develops in some cases when the insulin is injected at the same site over a period of as little as four weeks. In other cases it may take months to appear. It may occur after the use of any type of insulin and is unrelated to the dosage and concentration.

The cause of this lipotrophy is unknown. There has been no satisfactory explanation to account for the complication although several theories have been propounded. Among the possible factors

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LIPOTROPHY—COLLENS, BOAS, ZILINSKY AND GREENWALD

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abdomen and buttocks. In desperation and not knowing where else to inject her insulin, she inquired about the possible harm that might come from injecting insulin into the lipotrophic areas. There did not appear to be any serious objection so reinjection of these depressed areas. The patient

and has practically recovered from all her deformities.

We have since advised 6 other patients suffering from insulin lipotrophy to inject their daily insulin doses repeatedly into the deepest portion of the depression and in all these cases have seen, in one



A



B

FIGURE 2. Case of Insulin Lipotrophy in a Three-Year-Old Boy Involving Both Buttocks.
A shows appearance before treatment. B shows appearance six weeks after treatment. (Note almost complete recovery.)

returned one month later, and it was surprising to find that one atrophic area, which the patient had not injected for two years, had, after repeated daily injections, filled out and returned to its normal configuration.

As a result of this experience, the patient has since reinjected all the scooped-out depressions

month's time, striking complete recovery from the deformities.

SUMMARY

A method for the successful treatment of insulin lipotrophy is briefly presented.





LIPODISTROFIA= ALTERAZIONE DELLO STRATO LIPIDICO DEL SOTTOCUTE



LIPOIPERTROFIA



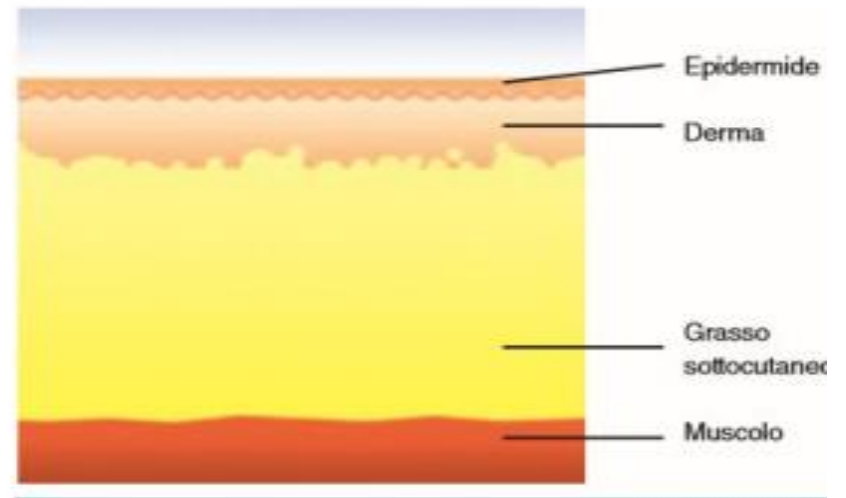
Media 38%
Variabili dal 2 al 75%



**LIPOIPOTROFIA o
LIPOATROFIA**



Oggi < 5 %

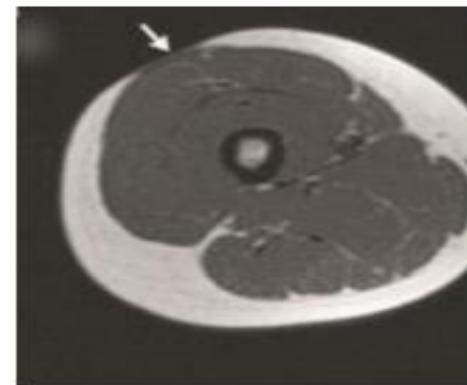




LIPOATROFIA

Avvallamento della pelle per atrofia del tessuto sottocutaneo

Descritta inizialmente in pazienti trattati con preparazioni insuliniche estrattive. Può insorgere da 2 mesi fino a 6 anni dopo l'inizio del trattamento insulinico





LIPOIPERTROFIA



Descritta come noduli sporgenti o piani di tessuto di consistenza duro gommosa, più o meno sporgenti sul piano della pelle circostante



EFFETTI DELLE LIPODISTROFIE

1. LH is very frequent
2. Main causes: insulin, non-rotation, reuse
3. LH distorts insulin absorption
4. LH worsens glucose control
5. LH leads to excessive and avoidable medical costs



LIPOHYPERTHOPHY PREVALENCE VARIABILITY

	Publication year	Prevalence (%)	Author	Diabetes type 1 or 2
Seyoum	1996	31.0	9	1 + 2
Hauner	1996	28.7	10	1
Partanen	2000	34.5	11	1
Raile	2001	27.1	12	1
Kordonouri	2002	48.0	13	1
Vardar	2007	48.8	14	1 + 2
Hajheydari	2011	14.5	15	1 + 2
Teft	2002	57.0	16	1 + 2
Blanco	2013	64.0	17	1 + 2
Grassi	2014	49.0	18	1 + 2
McNally	1988	28.0	19	2
Hauner	1996	3.6	10	2



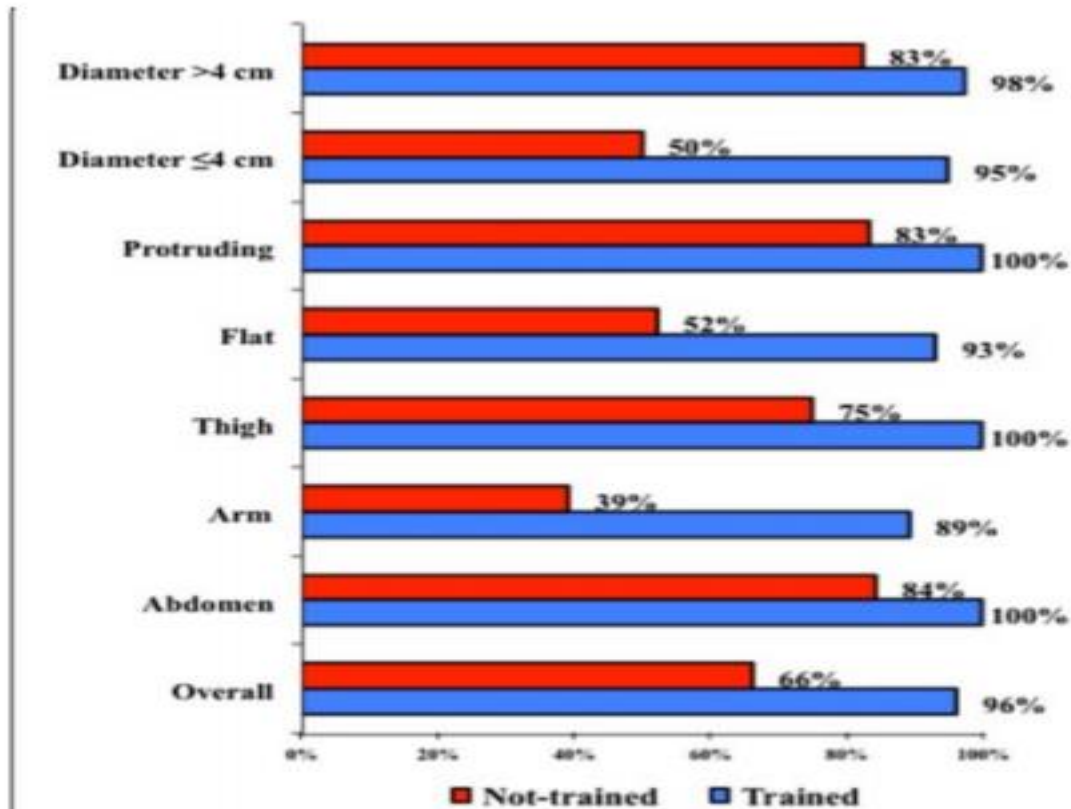
Rappresentazione schematica e caratteristiche clinico-morfologiche identificative dei tipi più frequenti di LH



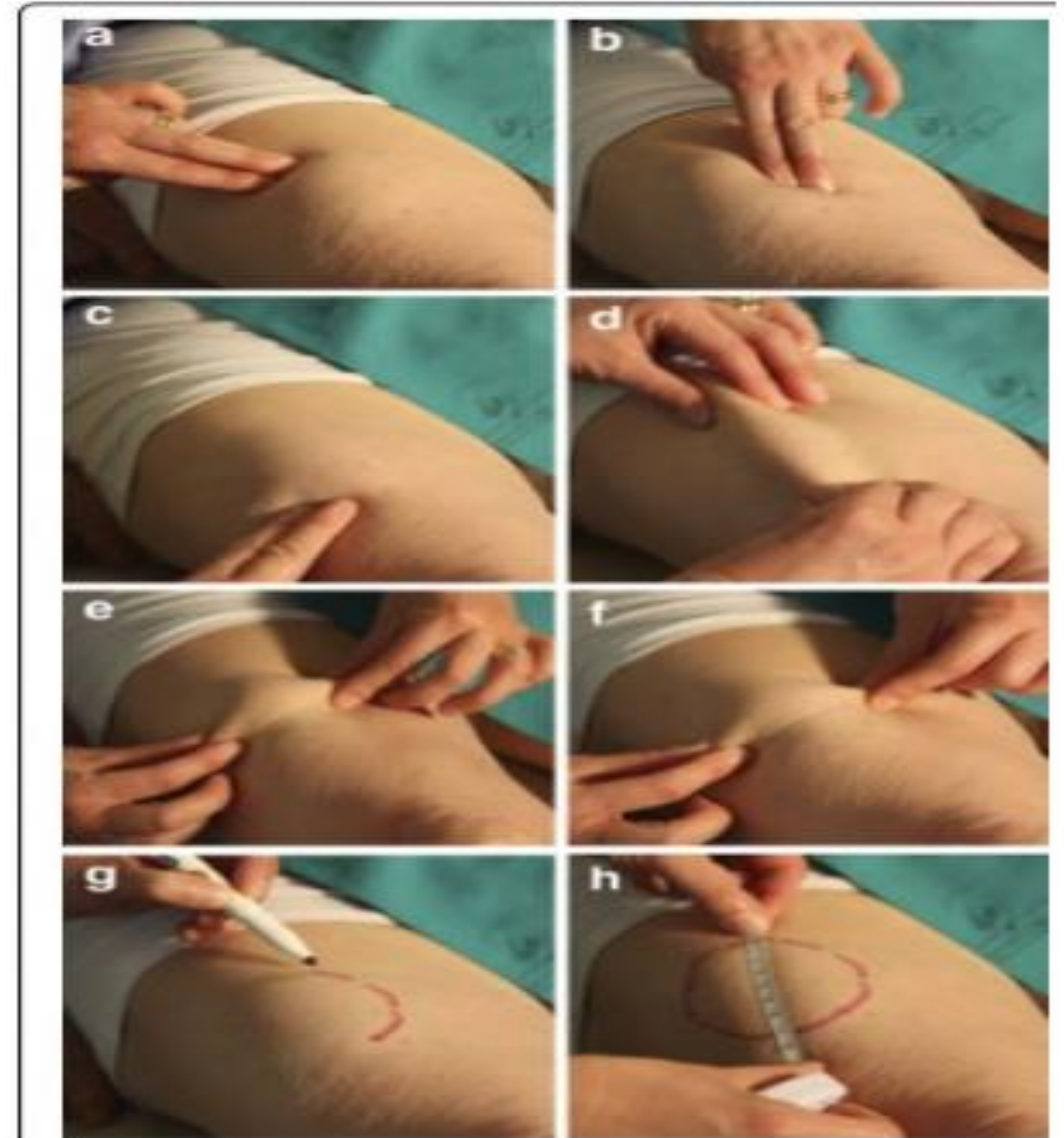
Tipo	Definizione	Visibilità	Palpabilità	Consistenza
A	Piccoli noduli	Facilmente evidente di profilo con luce tangenziale	Facile	Duro-elastica
B	Grandi noduli	Visibile di profilo, meglio con luce tangenziale	Facile	Duro-elastica
C	Piastrone duro-elastico	Visibile con difficoltà	Non facile/meglio definibile con pinching	Generalmente morbida
G	Nodulo molle	Non visibile	Difficile da distinguere/meglio con palpazione più vigorosa e/o pinching	Generalmente elastica



RICERCA DELLE LIPO-IPERTROFIE: METODOLOGIA

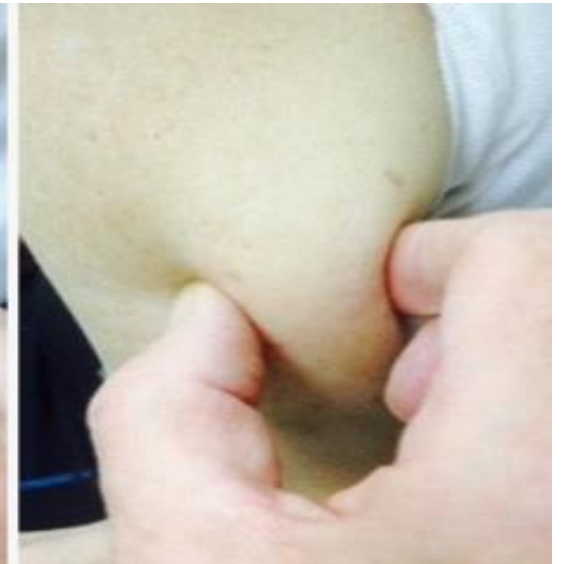


Lipohypertrophy identification results obtained by trained and non-trained health professionals as referred to the shape, site and size of skin lesions



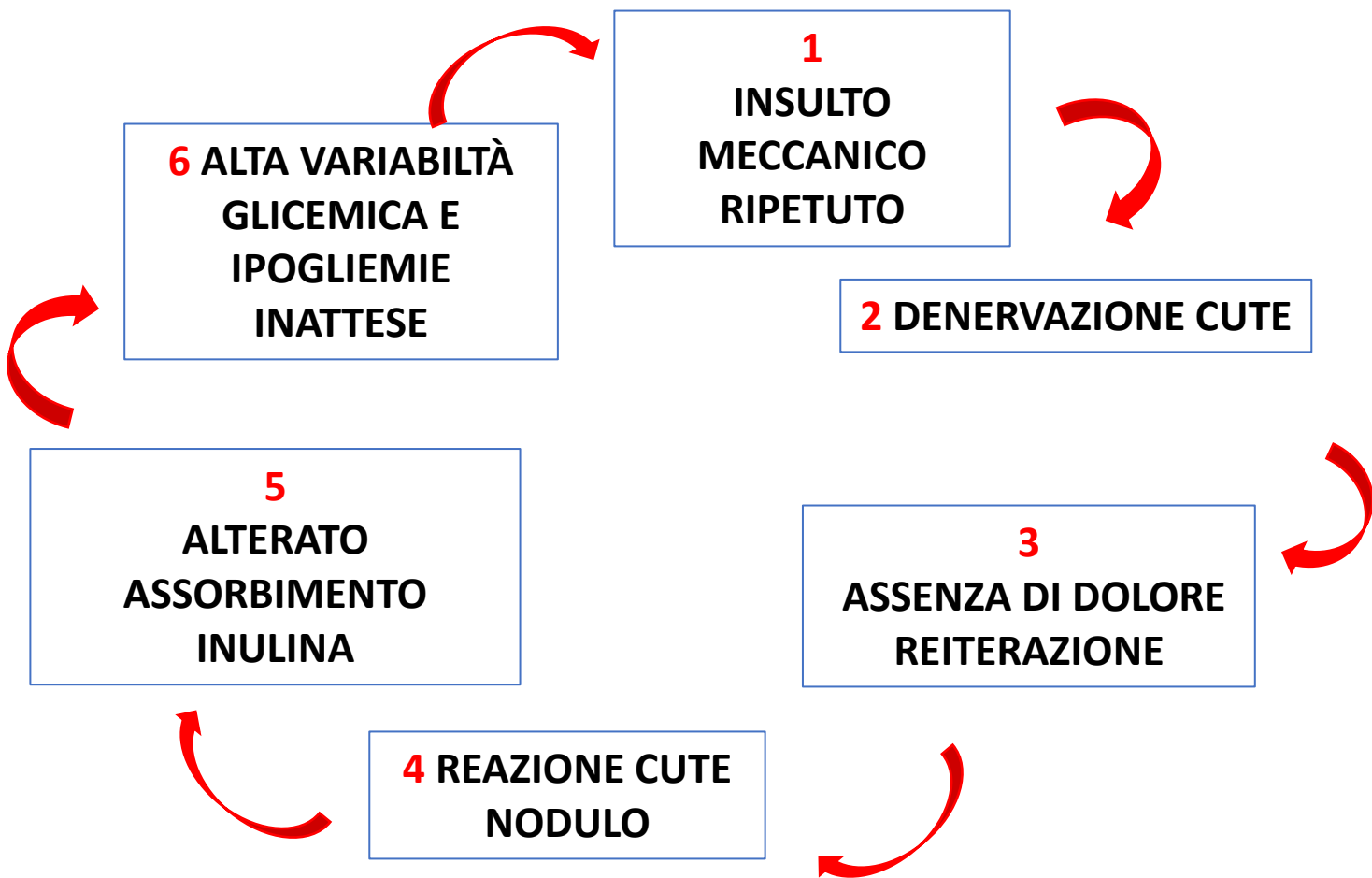


PINCHING



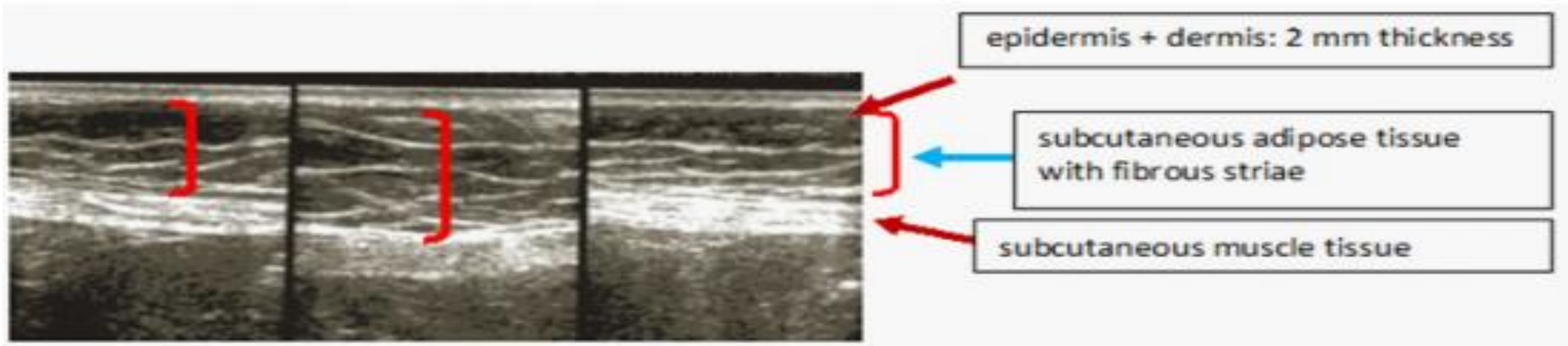
Le LIPO-IPERTROFIE variano dal 4,5% al 64%,

Ciò dipende da metodo, competenza e esperienza di chi le cerca



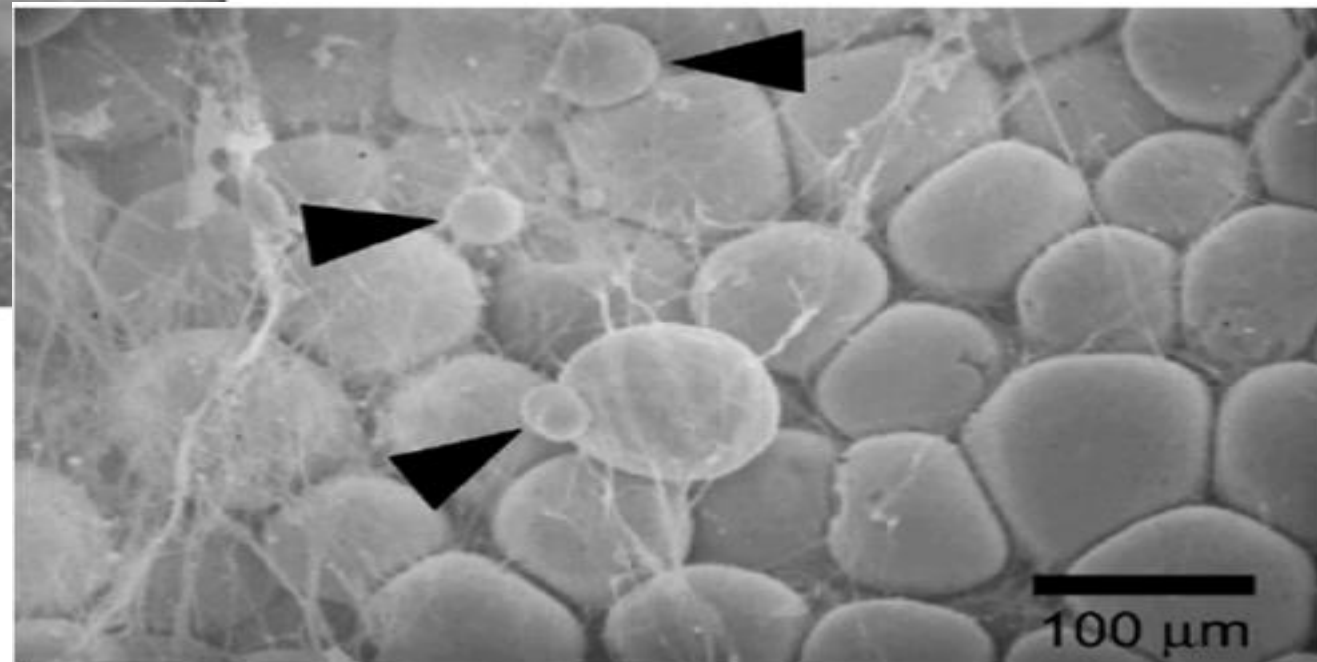
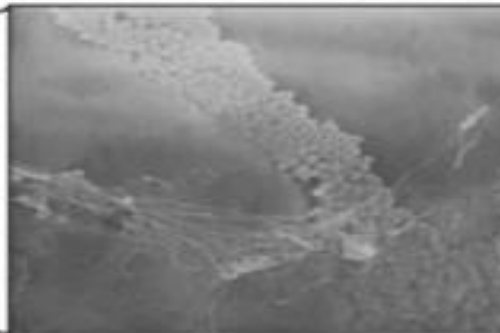
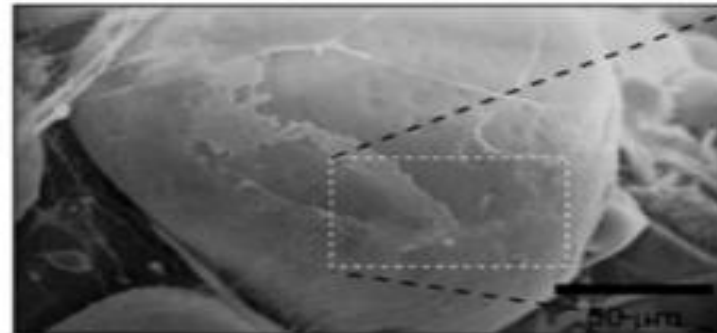
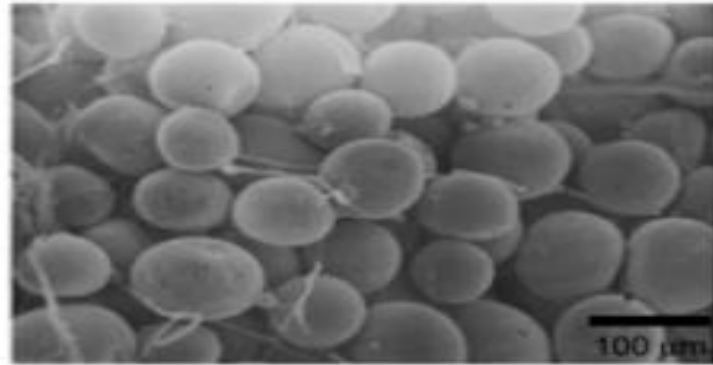
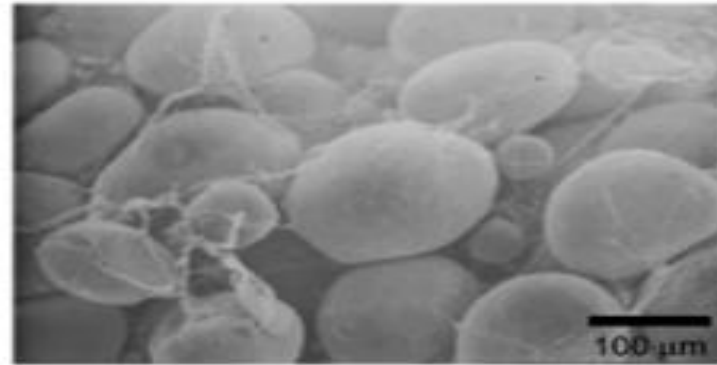


L'ecografia cutanea non è per uso clinico routinario ma può derimere dubbi e incertezze diagnostiche





**MICROSCOPIA ELETTRONICA DI NODULO LH
MEGA-ADICOPICI E MICRO-ADIPOCITI + AMPI TRALCI FIBROSI**





Frequency of LH and diabetes complications

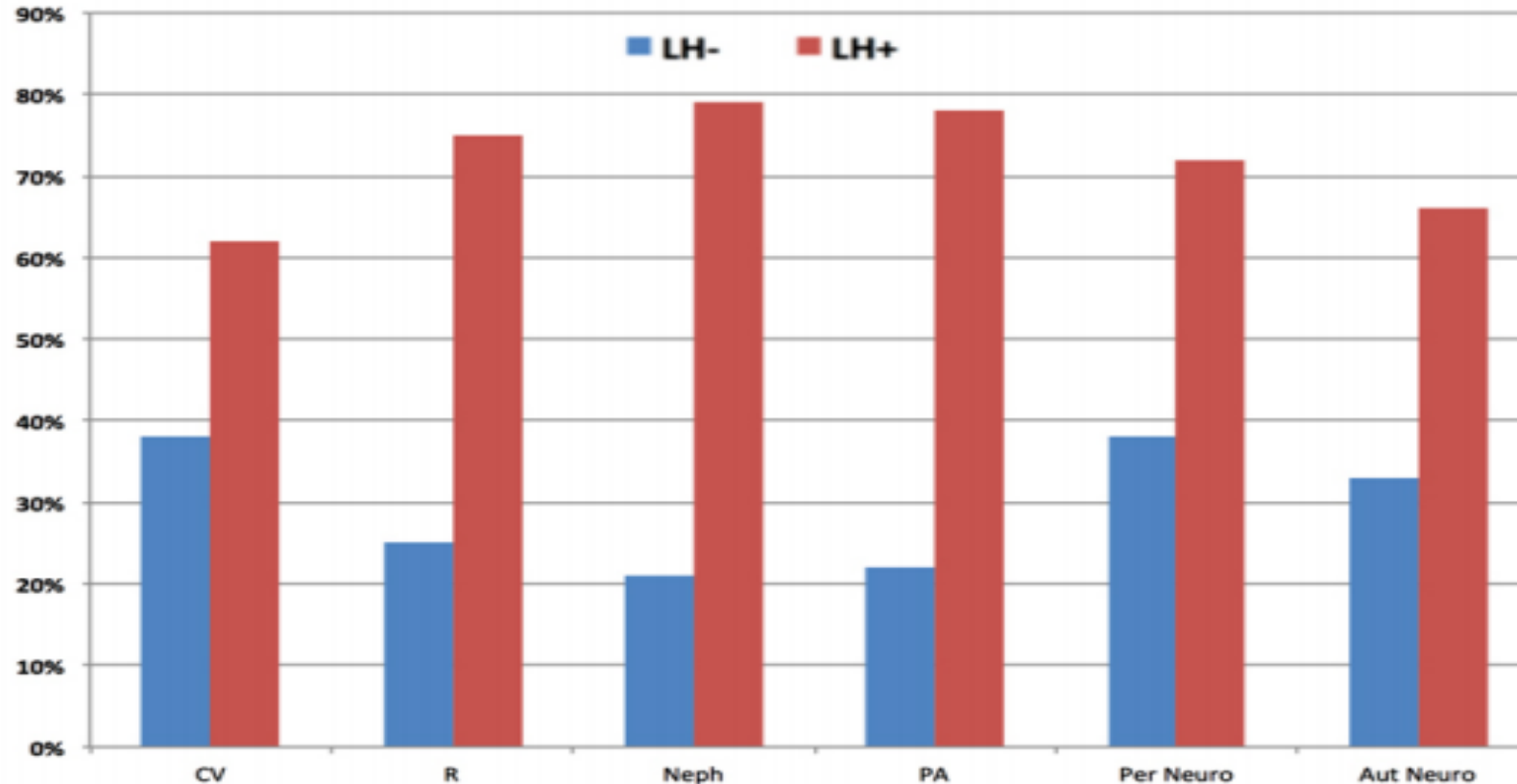


Figure 3: Frequency of LH and diabetes complications. All differences were statistically significant ($p < 0.001$).

CV: Cardio-CerebroVascular complications; R: Retinopathy, Neph: Nephropathy; PA: Peripheral Artery disease; Per Neuro: Peripheral Neuropathy; Aut Neuro: Autonomic Neuropathy.



RELATIONSHIP BETWEEN NEEDLE GAUGE AND LIPOHYPERTROPHY

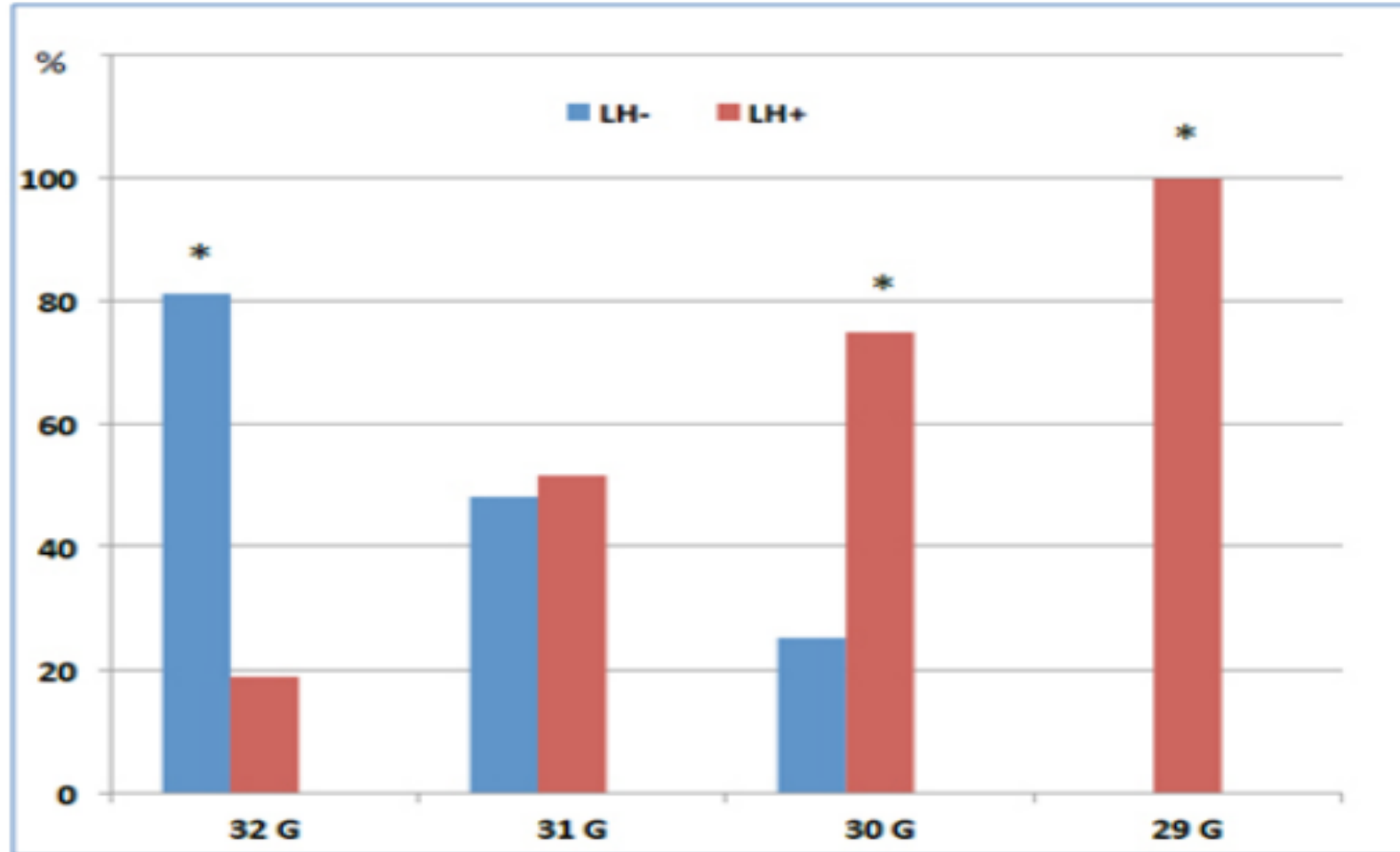
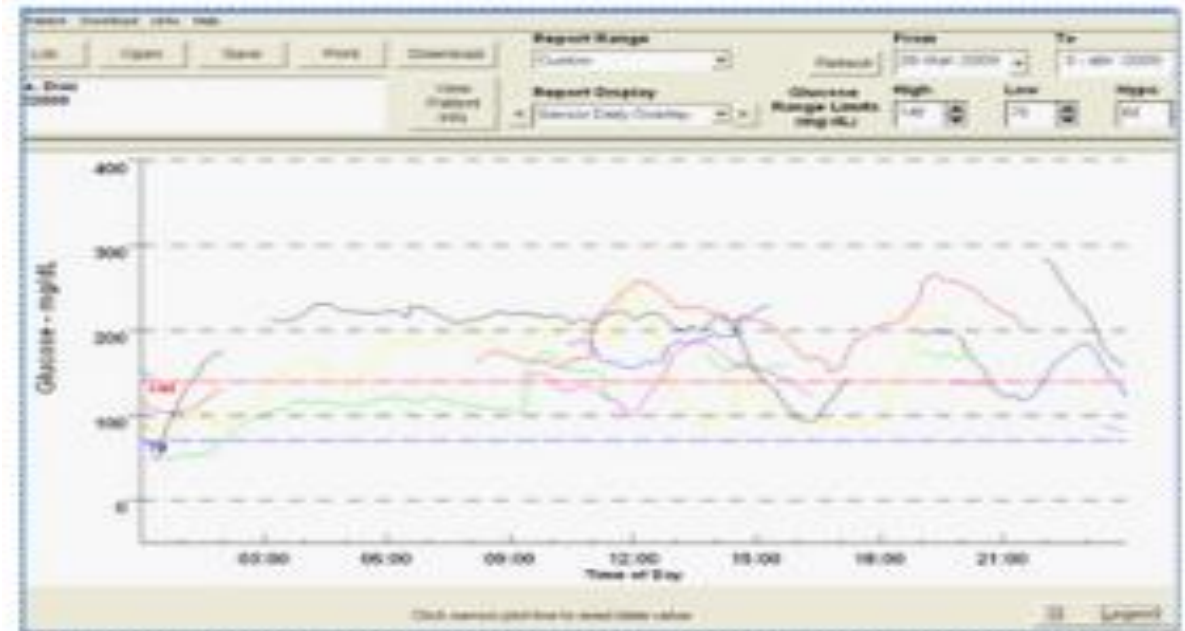
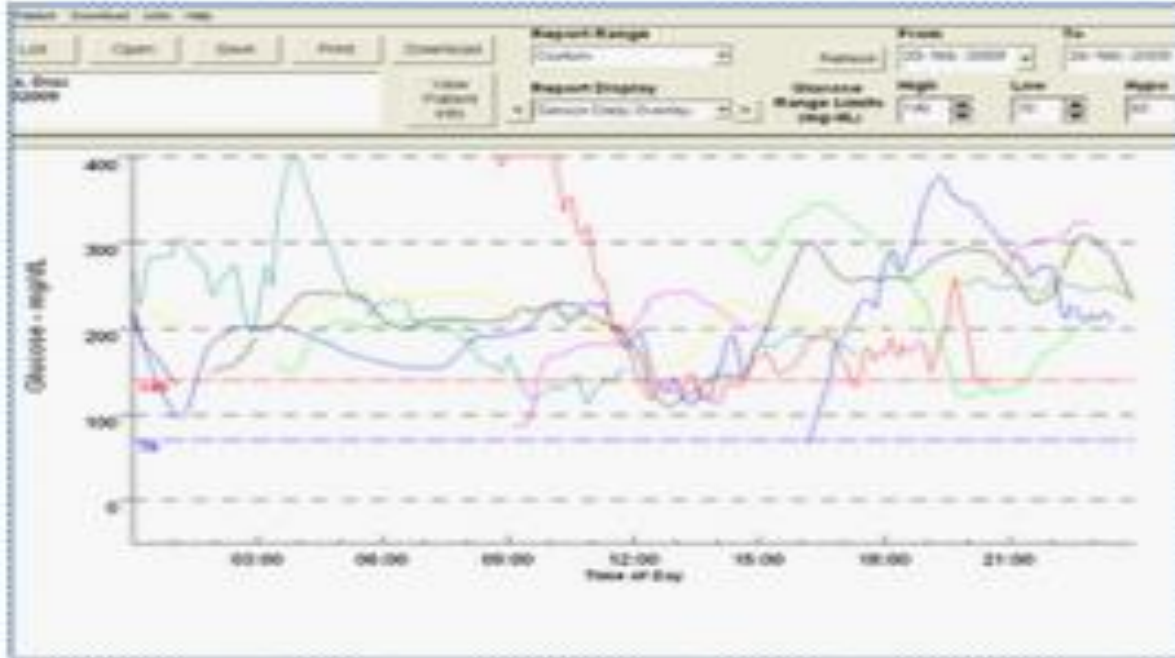


Figure 6: Relationship between needle gauge and lipohypertrophy. * $p < 0.001$.



VARIABILITÀ GLICEMICA



Contents available at [ScienceDirect](https://www.sciencedirect.com)Diabetes Research
and Clinical Practicejournal homepage: www.elsevier.com/locate/diabresInternational
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Federation

Cost saving effects of a short-term educational intervention entailing lower hypoglycaemic event rates in people with type 1 diabetes and lipo-hypertrophy

Sandro Gentile^a, Felice Strollo^{b,*}, on behalf of the Nefrocenter Research Study Group

198 persons T1DM and LH

Table 1 – Frequency and costs of severe and symptomatic hypoglycaemic events at baseline vs. post-education follow-up.

	Cost /event (€)	Severe hypos (Sevs)				Symptomatic hypos (Syms)			
		Baseline		Follow-up		Baseline		Follow-up	
		episodes n.	€	episodes n.	€	episodes n.	€	episodes n.	€
PHV	25.8	16	413.1	6 [*]	154.9	0	0	0	0
ER	241.0	49	11809.0	18 [*]	4338.0	0	0	0	0
EMS	128.5	49	6296.5	21 [*]	2698.5	0	0	0	0
FM/CWD	78.6	136	10689.6	42 [*]	3301.2	110	8646.0	42 [*]	3301.2
DHC	750.0	13	9750.0	6 [*]	4500.0	0	0	0	0
Total: €		38958.2		14992.6		8646.0		3301.2	

PHV = physician home visit; ER = emergency room visit and treatment; EMS = emergency medical service call/h; FM = family member; C = caregiver; WD = working day; DHC = daily hospitalization cost.

* $p < 0.01$ vs baseline.



DOPO 100 ANNI ANCORA COMBATTIAMO CON LE LIPODISTROFIE! E' TEMPO DI FARE DI MEGLIO !!!



Vittorio Emanuele II
1859 discorso al
parlamento
piemontese

2020, 26: 287

**Journal of Diabetes Research
Reviews & Reports**



Commentary

Open Access

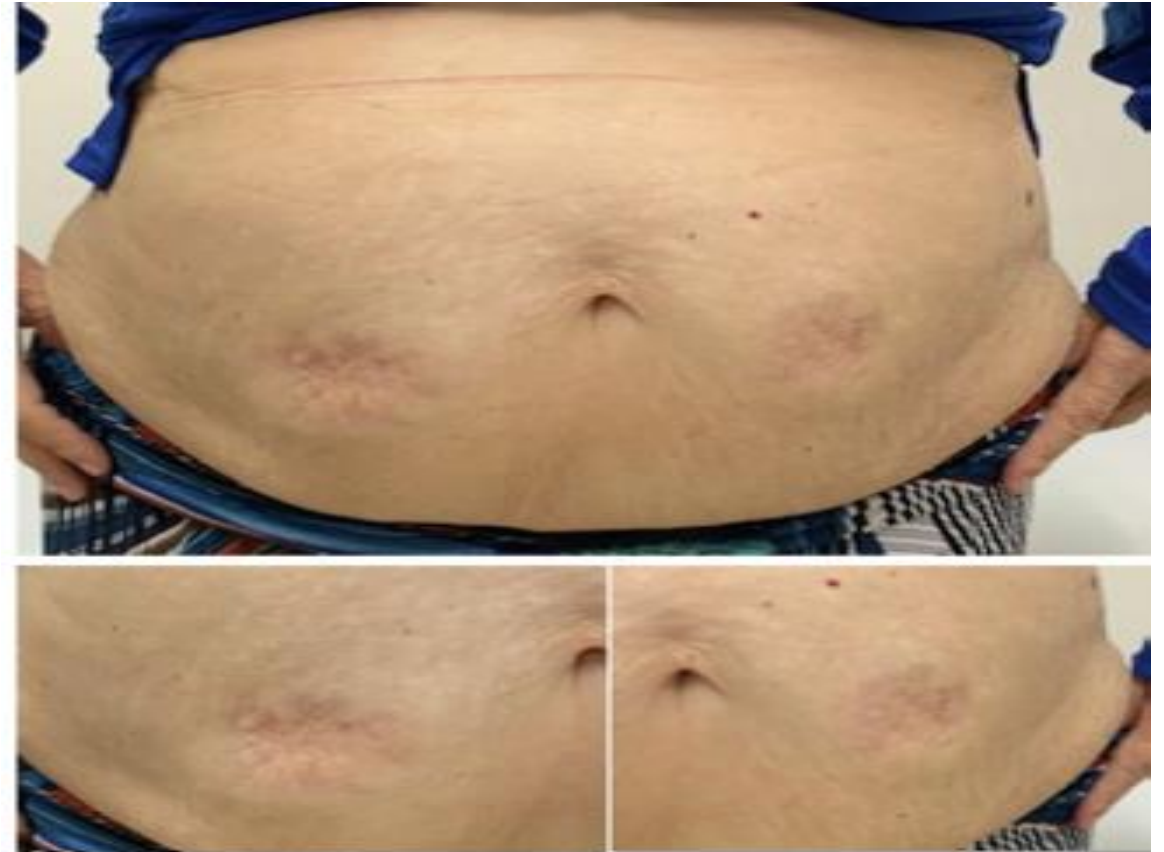
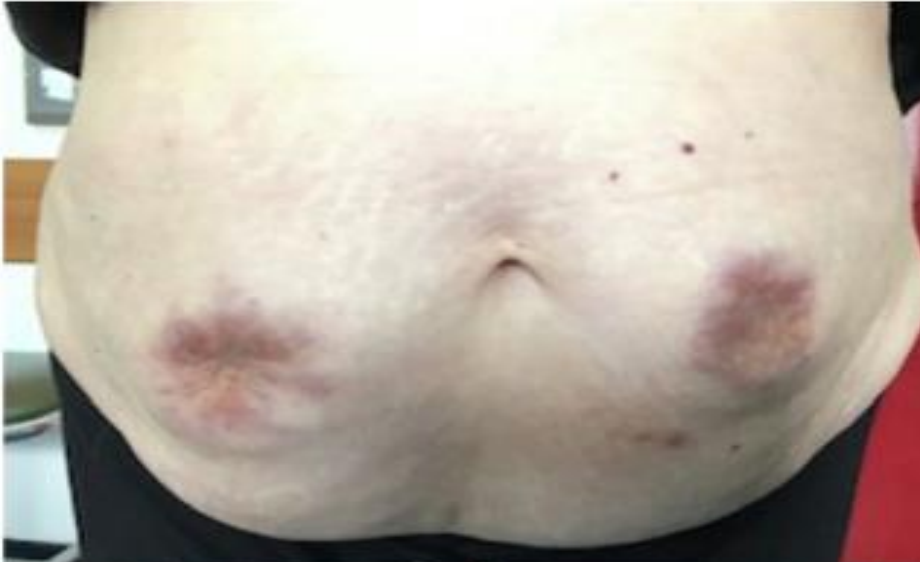
A Cry of Pain for Painless Insulin Lipohypertrophy

Sandro Gentile^{1*}, Giuseppina Guarino² and Felice Strollo³

1. Campania University "Luigi Vanvitelli", Naples, Italy
2. Nefrocenter Research & Nyx Start-Up Study Group Coordinator
3. Elle-Di and San Raffaele Research Institute, Rome, Italy



Tre anni dopo aver smesso di iniettare nei noduli



Liquido con insulina 13 volte più concentrata del sangue



Anno 63 a.C.

Quando, le Persone con diabete potranno vedere che Medici, Infermieri, Corsi di Laurea, di Specializzazione, Linee Guida, Raccomandazioni, Produttori di Insulina, Grandi Trials, Istituzioni smetteranno di parlare solo degli effetti “*teorici*” dell’insulina e si porranno il problema dell’educazione delle persone con diabete al corretto uso dell’insulina?

Ci vorranno altri 100 anni?

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