frequently display insulin resistance and compensatory hyperinsulinemia. In vivo overexposure to non-esterified fatty acids (NEFA) was shown to cause insulin resistance and androgen excess in humans, and our group found that bovine adrenal fasciculata cells overexposed in vitro to palmitate increases their androgen secretion. We thus hypothesized that overexposure of theca cells to NEFA would trigger insulin stimulation of androgen secretion.

Methods: Bovine theca cells were exposed for 48 hours to palmitate (saturated FA, 25 μM) and/or oleate (unsaturated FA, 50 μM) or vehicle (BSA); ±insulin (0–10,000 ng/mL) and ±forskolin (Fsk; 10 μM; which activates LH pathway). The androgen androstenedione (A4; ELISA) and a lipid peroxidation marker, 8-isoprostane (ELISA), were measured in culture media.

Results: Fsk increased theca cells A4 production for all insulin doses (all $p<0.05$). With Fsk, cell exposure to the palmitate/oleate mixture increased A4 production only in response to insulin stimulation (insulin 100–1000 ng/mL; at optimal dose of 500 ng/mL: 43±17% increase over Fsk, $p=0.03$). Palmitate alone did not affect A4 production, and oleate alone was not as effective as the palmitate/oleate mixture. Under Fsk treatment, palmitate increased 8-isoprostane production by 123±58% ($p=0.03$), which was unchanged using palmitate/oleate (4±15% over Fsk alone; p=NS).

Conclusion: This study found that theca cells overexposure to NEFA induces a significant stimulation of androgen production by insulin, under LH pathway activation. These results support a role of lipotoxicity and insulin in ovarian androgen overproduction, the main characteristic of PCOS.

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TSH Suppression Post-Therapy in Graves' Disease: A Systematic Review on Pathophysiology and Clinical Data

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Background: TSH can remain suppressed in patients with Graves' disease following treatment, making the titration of thyroid supplements difficult. TSH receptors have also been proven to exist on the folliculostellate cells of the pituitary gland, allowing the auto-antibodies of Graves' patients to create a paracrine effect that further lowers TSH levels.

Objectives: (1) To systematically evaluate the clinical data in the literature on TSH suppression post-therapy in Graves' disease and (2) to explore the data on the effect of TBII positivity on this issue.

Method: A systematic literature search was performed using EMBASE and PubMed databases, with several combinations of MeSH terms.

Results: Studies examining the recovery of TSH levels illustrated more prolonged suppression despite achieving clinical and biochemical euthyroidism. Data analysis illustrates that only 14.4% of patients had recovered their TSH less than 3 months after treatment. At 3 months, 47.5% of patients demonstrated TSH recovery, whereas 71% had recovered by 6 months ($p<0.001$). TBII was a determinant of TSH recovery at 6 months. Analysis shows 58% of patients with positive TBII recovered their TSH compared with 76% of TBII-negative patients at 6 months ($p=0.015$).

Conclusion: This analysis illustrates that TSH suppression can continue up to at least 6 months in a significant proportion of the patients with Graves' disease post-therapy. Also, TBII activity can be a predictor of prolong TSH suppression, as analysis demonstrates a significant difference between the groups. This may be helpful clinically to predict TSH recovery, and its reliability when titrating thyroid supplements.

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Efficacy and Safety of Once Weekly Dulaglutide vs. Insulin Glargine in Combination with Metformin and Glimepiride in Type 2 Diabetes Patients (AWARD-2)

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Background and aims: This phase 3, parallel-arm, open-label, 78-week study compared the once weekly GLP-1 receptor agonist dulaglutide (DU) with insulin glargine titrated to target in combination with maximal tolerated doses of metformin and glimepiride in patients with type 2 diabetes. The primary objective was to show non-inferiority of DU 1.5 mg versus glargine on HbA1C change from baseline at 52 weeks.

Materials and methods: Patients (n=807, mean baseline characteristics: age 57 years, HbA1C 8.1%, weight 86.34 kg) were randomized (1:1:1 ratio) to DU 1.5 mg, DU 0.75 mg or glargine.

Results: DU 1.5 mg was superior at 52 (−1.08%) and 78 weeks (−0.9%) in A1C change from baseline to glargine (−0.63% and −0.59% at 52 and 78 weeks, respectively) and DU 0.75 mg (−0.76% and −0.62% reduction at 52 and 78 weeks) was noninferior to glargine; weight decreased with both DU doses and increased with glargine. At 78 weeks, mean rates of documented symptomatic hypoglycemia (≤3.9 mmol/L) were lower in each DU arm vs. glargine (1.7, 1.7 and 3.0 events/pt/y for DU 1.5 mg, DU 0.75 mg and glargine, respectively) ($p\leq0.002$, both); severe hypoglycemia was minimal with DU and glargine; nausea and diarrhea were more common with DU 1.5 mg (15.4%, 10.6%) and DU 0.75 mg (7.7%, 9.2%) vs. glargine (1.5%, 5.7%).

Conclusion: DU 1.5 mg demonstrated superior, and DU 0.75 mg noninferior glycemic control compared to glargine with an acceptable safety profile.

Primary endpoint (52 weeks, ITT, LOCF)	DU 1.5 mg (n=273)	DU 0.75 mg (n=272)	Glargine (n=262)
A1C change (%), LS mean (SE)	−1.08 (0.06)[†,††]	−0.76 (0.06)[†]	−0.63 (0.06)
% pt with A1C <7.0%	53.2[#]	37.1	30.9
Weight change (kg), LS mean (SE)	−1.87 (0.24)[#]	−1.33 (0.24)[#]	1.44 (0.24)
Final endpoint (78 weeks, ITT, LOCF)			
A1C change (%), LS Mean (SE)	−0.90 (0.07)[†,††]	−0.62 (0.07)[†]	−0.59 (0.07)
% pt with A1C <7.0%	49.0[#]	34.1	30.5
Weight change (kg), LS Mean (SE)	−1.96 (0.26)[#]	−1.54 (0.26)[#]	1.28 (0.26)

[†,††] multiplicity adjusted 1-sided $p<0.001$ for noninferiority or superiority vs. glargine, respectively, for A1C change
[#] 2-sided $p<0.05$ vs. glargine

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Liraglutide and the Preservation of Pancreatic Beta-Cell Function in Early Type 2 Diabetes: The LIBRA Trial

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Background: Clinical studies evaluating the effects of medications on beta-cell function in type 2 diabetes (T2DM) are compromised by an inability to determine the actual baseline degree of beta-cell dysfunction, independent of the reversible dysfunction induced by hyperglycemia (glucotoxicity). Short-term intensive insulin therapy (IIT) is a strategy for eliminating glucotoxicity before